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Systematic review

Smoking Cessation and Risk of Esophageal Cancer by Histological Type: Systematic Review and Meta-analysis

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Abbreviations used in this paper: CI, confidence intervals; RR, risk ratio; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

ABSTRACT

Background: Tobacco smoking strongly increases risk of esophageal squamous cell carcinoma and moderately increases risk of esophageal adenocarcinoma. How smoking cessation influences esophageal cancer risk across histological subtypes, time latencies, and geographic regions is not clear.

Methods: Studies were systematically searched on Medline, Embase, Web-of-Science, Cochrane Library, and ClinicalTrial.gov. Pooled estimates of risk ratios (RRs) were derived using random effects model. Cochran's Q test and I^2 statistic were used to detect heterogeneity.

Results: Among 15,009 studies, 52 fulfilled the inclusion criteria. Using non-smokers as reference, risk of esophageal squamous cell carcinoma was lower among former smokers (RR=2.05, 95% confidence intervals (CI) 1.71-2.45) than among current smokers (RR=4.18, 95% CI 3.42-5.12). Compared with current smokers, a strong risk reduction was evident ≥5 years (RR=0.59, 95% CI 0.47-0.75), and became stronger ≥10 years (RR=0.42, 95% CI 0.34-0.51) and ≥20 years (RR=0.34, 95% CI 0.25-0.47) following smoking cessation. The risk reduction was strong in Western populations, while weak in Asian populations. Using non-smokers as reference, the risk of esophageal adenocarcinoma was only slightly lower among former smokers (RR=1.66, 95% CI 1.48-1.85) than among current smokers (RR=2.34, 95% CI 2.04-2.69). The risk of esophageal adenocarcinoma did not show any clear reduction over time after smoking cessation, with RR of 0.72 (95% CI 0.52-1.01) ≥20 years after smoking cessation, compared with current smokers.

Conclusions: Smoking cessation time-dependently decreases risk of esophageal squamous cell carcinoma, particularly in Western populations, while it has limited influence on the risk of

esophageal adenocarcinoma.

Esophageal cancer is the 9th most common cancer and the 6th leading cause of cancer death globally (1). The overall prognosis is poor (<20% 5-year survival) and has not improved much despite intensive research aiming to develop the treatment, which stresses the need for preventive actions. Esophageal cancer has two main histological subtypes, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). ESCC accounts for 80% of cases globally and is the dominant subtype in Asian countries (2). In many Western countries, however, the incidence of EAC has increased rapidly during the last four decades and now exceeds that of ESCC (3, 4).

Tobacco smoking and heavy alcohol consumption are the main risk factors for ESCC, particularly in Western populations (5). Dietary factors, socioeconomic status, exposure to environmental carcinogens, and inherited susceptibility may play a stronger role in etiology of ESCC in Asian populations compared with Western populations (6-8). The main risk factors for EAC are gastroesophageal reflux disease and obesity, while tobacco smoking is only a moderately strong risk factor (9-11). However, these studies are base d on Western populations. In Asia, on the other hand, the incidence rate of EAC remains low and the etiology of EAC has rarely been studied (12).There is a dose-response association between smoking and both subtypes of esophageal cancer, and 49% of ESCC cases are estimated to be attributable to smoking (13-15). Although one literature review and one pooled analysis of 12 studies indicated a decreased risk of esophageal cancer following tobacco smoking cessation (14, 16), it is not clear how smoking cessation influences the risk of esophageal cancer across histological subtypes, time latencies between cessation and risk reductions, and geographic areas globally. Yet, such knowledge should be of great importance for public health and healthcare. Therefore, we conducted a systematic review and meta-analysis which, to the best of our knowledge, is the first study aiming to clarify the role of smoking cessation in relation to the risk of esophageal cancer with separate assessments of the main histological subtypes, time latencies, and geographic regions.

Methods

Search strategy and selection criteria

This systematic literature review and meta-analysis was performed in accordance with the PRISMA statement and MOOSE guidelines (17, 18). The search strategy was discussed and a final search string was agreed upon by all authors. A systematic search was conducted on MEDLINE, Embase, Web-of-Science and Cochrane Library databases (up to March 30, 2016) for studies reporting data on the association between tobacco smoking cessation and the risk of esophageal cancer. For the search, we used a combination of three themes of Medical Subject Headings terms and related extended versions: “smoking or tobacco”, “esophageal or oesophageal”, and “cancer, squamous cell carcinoma or adenocarcinoma”. No restrictions in the search strategy were used. Reports on ongoing registered clinical trials from the National Institute of Health website (http://www.clinicaltrials.gov) were also considered. In addition, we reviewed the reference lists of original studies, review articles, systematic reports, and the two monographs on “Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines” and “Tobacco Smoking and Involuntary Smoking” by the International Agency for Research on Cancer (IARC) to identify further studies of potential interest (19, 20). The search strategy is presented in more detail in the **Supplementary Methods**.

Studies fulfilling the following criteria were considered for inclusion in the systematic review: 1) smoking status was ascertained and data were presented as odds ratios (OR), risk ratios (RR), hazard ratios (HR), or in another format from which the relative risk could be estimated; 2) case-control studies, cohort studies, intervention studies, and clinical trials; and 3) original and independent studies with full text. Language restriction was implemented only at the end of the search when only studies published in English were eligible. In the case of multiple reports on the same study population, only the most recent or most informative report with the longest follow-up was considered. We followed a detailed study protocol that was completed before initiation of the search for eligible studies.

One reviewer (Q.L. Wang) conducted the initial search and removed obviously irrelevant articles by screening the titles and abstracts according to the selection criteria. The final decision of articles selected for the review was made by all authors. We contacted the investigators for relevant data if their studies were potentially eligible for this study.

Data extraction and quality assessment

Identified studies were independently assessed by two authors (Q.L. Wang and W.T. Li) and any discrepancies were resolved by joint review of reports to reach consensus, or determined by a third author (S.H. Xie). The following information was collected from the eligible studies into an electronic database: author names, year of publication, geographic origin, number of participants, number and type of case patients (incident or prevalent), participants' characteristics (ethnic origin, mean age, and sex), histological subtype of esophageal cancer (squamous cell carcinoma or adenocarcinoma), method of ascertainment of case patients, smoking status (non-, former, or current, and years since smoking cessation), control for potential confounding factors (by matching or statistical analysis), and statistical analysis. For case-control studies, we collected information on participation rates and how control subjects were recruited. For cohort studies and clinical trials, information of representativeness of the study participants and the completeness, period, and duration of follow-up were recorded.

The methodological quality of the studies was assessed in terms of selection bias, information bias, and bias from confounding. We quantitatively scored the study quality according to the nine-item Newcastle-Ottawa Scale (21), which includes assessment of the generalizability of the study population, selection of control subjects or non-exposed cohort members, exposure, definition of control subjects or participants at the start of the cohort, adjustment for relevant confounders, outcome, response rate or completeness of follow-up, and rate of loss to follow-up or drop-outs. An additional item was added to the scale, i.e. if smoking was investigated as the main exposure (1 point) or as a confounding variable only (0 point) (22). The methodological quality assessment could provide a score from 0 to 10 on the final scale, where higher scores represent better quality.

Statistical analysis

Tobacco smoking status (current, former, or non-smoker) and time latencies of smoking cessation were analyzed in relation to the risk of ESCC and EAC separately. In most included studies, current smokers were defined as those who smoked at the time of recruitment into the study or those who stopped smoking less than one or two years before recruitment. Former smokers were defined as those who quit smoking one or two years before inclusion, although two studies used five years as the boundary for current and former smokers (23, 24). In the analyses of latency time after smoking cessation, some studies used current smokers as the reference group, while other studies used non-smokers. Therefore, in the meta-analysis, the reference groups were all uniformed to current smokers for an easier understanding of smoking cessation, using method suggested by Hamling et al (25). We categorized smoking cessation latency into five groups: non- smokers, <5 years, 5-9 years, 10-20 years, or >20 years. Some studies reported more than one category of duration for the first 5 years or over 20 years after smoking cessation, e.g. multiple categories of <2 years and3-5 years for the first 5 years, or 20-29 years and >30 years for the over 20 years (26-29). In such cases, we combined these categories into a single one, i.e. <5 years or >20 years, according to the meta-analysis approach by pooling the estimates for these more than two categorizes into one estimates of the risk ratio (30).

RR was used as the measure of association in the meta-analysis. For some studies, HR and OR were used as proxies of RR, which was justified by the low incidence of esophageal cancer (30). To take heterogeneity into account, we used random effects model (Der-Simonian and Laird's method) to compute the pooled RRs and we also calculated their 95% confidence intervals (CIs) (31).

Statistical heterogeneity across studies was assessed by the Cochran's Q test (a P-value <0.10 being considered as statistically significant for conservativeness of the test) (32), and I^2 statistic which describes the proportion of the total variation in study estimates that is due to heterogeneity rather than by chance (33). An I^2 value of <25% indicated low heterogeneity, 25-

50% moderate, and >50% is suggestive of high heterogeneity (34). We conducted stratified analyses by study design (case-control or cohort study), publication year (≤1999, 2000-2009, or ≥2010), geographic origin of the study (North America, Europe, Oceania, Asia, or South America), gender (men, women or unspecified), response rate (≥80%, <80%, or unknown), smoking exposure (main exposure or confounder), tobacco type (cigarettes or unspecified), study quality (low with score <7 or high with score ≥7), potential confounding factors adjusted for (alcohol use, dietary factors, socio-economy, place of residence, body mass index, or gastroesophageal reflux). For case-control studies, we stratified analyses by study design (population-based or hospital-based), cases recruitment (incident, prevalent or unknown), and source of control subjects (neighborhood or unrelated). For cohort studies, we stratified for study design (population-based or hospital-based), follow-up time (<10 years or ≥10 years), and assessment of outcomes (record linkage or self-reported).

Publication bias was evaluated using Begg's and Egger's tests, as well as visual inspection of the funnel plots (35, 36). In addition, exploratory meta-regression was performed to examine potential sources of heterogeneity using the same covariates as in the stratified analysis, where P-values of <.10 were regarded statistically significant. We used sensitivity analyses by removing one study at a time to examine the robustness of the pooled RRs. The statistical analyses were conducted using the Comprehensive Meta-Analysis program version 3.3 (Biostat, Englewood, NJ, USA). All statistical tests were two-sided.

Results

Literature search and study characteristics

The search identified 15,009 studies. Among these, 52 studies fulfilled the inclusion criteria and were enrolled to this meta-analysis (**Figure 1**)(9, 23, 24, 26-29, 37-81). Of the 52 studies, 41 and 23 studies contained smoking data in relation to risk of ESCC and EAC, respectively. Most studies were case-control studies (n=44) including a total of 11,965 esophageal cancer cases and 47,817 control subjects, and the remaining (n=8) were cohort studies with 1,185 new esophageal cancer cases among 1,045,947 cohort members. No randomized clinical trials met the inclusion criteria. Most studies were conducted in Europe (n=22), the United States (n=10), and Mainland China or Taiwan (n=7), while the remaining studies were conducted in Japan (n=3), Brazil (n=3), Uruguay (n=3), Argentina (n=1), Australia (n=1), Czech Republic (n=1), and Serbia (n=1). Two studies from the United Kingdom were performed on the same study population, but analyzed the two eligible histological types of esophageal cancer in separate studies (45, 49). Two studies from Uruguay had partly overlapping study periods (52, 53). Some overlap of research centers was possible in three studies from Italy or Switzerland (44, 47, 48), and two studies from Taiwan were partly overlapping (57, 75). **Supplementary Tables 1 and 2** provide an overview of characteristics of the included case-control studies and cohort studies, respectively.

Quality assessment

A detailed study quality assessment is shown in **Supplementary Tables 3-5**. In brief, of all 41 studies examining ESCC, 22 (53.7%) had a high quality score (≥7) and 19 (46.3%) had a lower quality score (<7). Of all 23 studies analyzing EAC, 17 (73.9%) had a high quality score (≥7) and 6 (26.1%) had a lower quality score (<7). Thirty (57.7%) of all 52 studies reported different categories of years after smoking cessation, including 18 analyzing ESCC and 12 analyzing EAC. Among these, one study analyzing EAC did not report more categories than <26 years of smoking cessation, and was therefore not included in the further analysis (23). Detailed results by duration since smoking cessation in the original studies are presented in **Supplementary Table 6**. Eighteen (34.6%) studies reported sex-specific associations. All but 10 (19.2%) studies examined tobacco smoking as the main exposure. Among the 44 case-control studies, 16 were population-based and 31 analyzed incident cancer cases. Among the cohort studies, all but one identified case patients via record linkages and the longest follow-up was 22.2 years. Adjustment for age and sex was made in all studies except for one (76). Adjustments for other potential confounding factors in the included studies are shown in **Supplementary Table 3**.

Smoking cessation and esophageal squamous cell carcinoma

In an analysis of the 41 studies assessing ESCC, former smokers had an RR of 2.05 (95% CI 1.71-2.45, **Figure 2**), and current smokers had an RR of 4.18 (95% CI 3.42-5.12, **Supplementary Figure 1**), compared to non-smokers. There was a dose-response association between smoking cessation latency time and risk of ESCC (**Figure 3A**). Compared to current smokers, those who had quit smoking <5 years ago had an RR of 0.96 (95% CI 0.73-1.25), and those who had quit smoking 5-9 years, 10-20 years, and >20 years ago had RRs of 0.59 (95% CI 0.47-0.75), 0.42 (95% CI 0.34-0.51), and 0.34 (95% CI 0.25-0.47), respectively (**Figure 3A, Supplementary Figure 2**). The RR for those who quit smoking >20 years ago was similar to that of non-smokers with an RR of 0.22 (95% CI 0.18-0.28). In a sensitivity analysis restricted to studies that reported RRs of all smoking cessation latency categories, the results were similar to those of the overall analyses (**Supplementary Table 7**). The meta-analysis revealed substantial heterogeneity across studies for RRs in former smokers (I^2=69.6%, P<.001) and current smokers (I^2=85.0%, P<.001).

The results from the stratified analyses are shown in **Table 1**. All RRs in former smokers were lower than RRs in current smokers in each stratum for ESCC, although heterogeneity (I^2>50%) was found in most strata. The difference in RR between former smokers and current smokers was most pronounced in studies from North America and Europe, while it was not evident in Asian studies. Among former smokers, women had lower RRs of ESCC than men. High quality studies (score ≥7) generated higher RRs of ESCC among current smokers and lower RRs among former smokers, compared with low quality studies (score <7). The results remained stable after adjustment for alcohol use and dietary factors. In hospital-based case-control studies, the RRs among both former and current smokers were slightly higher compared to population-based studies (**Table 1**).

The meta-regression showed that sex and study quality could explain 11.0% (P=.08) and 13.6% (P=.06) of the heterogeneity in former smokers, respectively (data not shown). The continent where the study was conducted and source of controls (neighborhood-based or unrelated) could explain 9.1% (P=.02) and 19.1% (P=.01) of the heterogeneity in current smokers, respectively. The sensitivity analyses excluding one study at a time showed no substantial changes (**Supplementary Figure 3 and 4**).

Smoking cessation and esophageal adenocarcinoma

In an analysis of all 23 studies, former smokers had an RR of 1.66 (95% CI 1.48-1.85, **Figure 4**) and current smokers had an RR of 2.34 (95% CI 2.04-2.69, **Supplementary Figure 5**), compared to non-smokers. No substantial heterogeneity of the RRs was revealed for former smokers (I^2=11.6%, P=.30) or current smokers (I^2=26.0%, P=.13). Studies from North America (n=10) showed the highest RR among former smokers (RR=1.87, 95% CI 1.62-2.16) and current smokers (RR=2.52, 95% CI 2.14-2.96), compared to studies from other continents (**Supplementary Table 8**).

Compared to current smokers, smoking cessation <5 years ago was associated with an RR of 0.81 (95% CI 0.52-1.26), 5-9 years with an RR of 0.87(95% CI 0.58-1.30), 10-20 years with an RR of 0.95(95% CI 0.78-1.15) and >20 years ago with an RR of 0.72 (95% CI 0.52-1.01) (**Figure 3B**, **Supplementary Figure 6**).

Publication bias

No publication bias was detected by visual inspection of the funnel plot or by the Begg's and Egger's test (**Supplementary Figure 7**). For ESCC, P-values for former smokers using Begg's and Egger's test were .17 and .19, respectively. The corresponding P-values for current smokers were .09 and .20, respectively. Similarly, no publication bias was found for EAC. The P-values for former smokers using Begg's and Egger's test were .71 and .63, respectively. The corresponding P-values for current smokers were .81 and .33, respectively.

Discussion

This study indicates a strongly decreased risk of ESCC in former smokers compared to current smokers, and a clear decline in risk of ESCC already within 5 years of smoking cessation, which further decreased with each longer latency period of smoking cessation until after 20 years, when the risk was similar to that of non-smokers. North American populations seem to benefit most from smoking cessation, while Asian populations benefitted the least. There was only a small difference in the risk of EAC comparing former and current smokers, and a slightly decreased risk of EAC was suggested only among those who had stopped smoking over 20 years ago. The observed associations of the risk of ESCC or EAC in current or former smokers persisted across subgroups stratified by participants´ characteristics and study design.

This meta-analysis has several main strengths, including the extensive search strategy which should have identified all relevant publications globally. It includes a large number of studies and participants, which provides good statistical power for robust subgroup analyses, including separate analyses of the main histologic types of esophageal cancer and various lengths of smoking cessation periods. There are also limitations; heterogeneity was found across studies investigating the risk of ESCC for former and current smokers. This might have resulted from the large number of included studies, differences in design, population, and quality of the studies, as well as differences in participants' characteristics. To reduce the influence of heterogeneity, random effects model was used. All stratified analyses showed decreased RRs among former smokers compared with current smokers. In analyses restricted to higher study quality studies, the decrease in RR was greater between current and former smokers, indicating the robustness of the findings. The restriction of studies to those published in the English language with full text might have resulted in the exclusion of some small or low quality studies. However, the results were unlikely affected by any such exclusion since no publication bias was detected. Finally, biases of observational studies cannot be avoided, but the results from cohort studies revealed similar results as those from case-control studies, which indicate robustness. Moreover, the risk reductions seen after smoking cessation are biologically plausible.

To the best of our knowledge, this is the first systematic review and meta-analysis estimating the influence of smoking cessation on the risk of esophageal cancer by histological type. Yet, the decreased risk of ESCC among former smokers compared to current smokers is consistent with the results of a meta-analysis of 15 Japanese studies, showing an RR of esophageal cancer 3.73 (95% CI 2.16-6.43) in current smokers and 2.21 (95% CI 1.60-3.06) in former smokers (82). Although the histologic type of cancer was not provided in that study, the vast majority of patients with esophageal cancer in Japan have ESCC. Regarding EAC, our results are similar to a meta-analysis that included studies published before January 2010, implying an RR of esophageal and gastric cardia adenocarcinoma combined of 2.32 (95% CI 1.96-2.75) in current smokers and 1.62 (95% CI 1.40-1.87) in former smokers (83). However, due to the limited statistical power, separate analysis of EAC (excluding cardia cancer) was not possible in that study (83). A pooled analysis of 12 studies suggested benefits of smoking cessation for EAC after 10 years (odds ratio 0.71, 95% CI 0.56-0.89) (14). However, the risk of EAC following smoking cessation of 10-20 years or more than 20 years was not assessed in that study (14). The present meta-analysis showed that any benefit from smoking cessation became evident only more than 20 years after smoking cessation, which is in agreement with opinions from two literature review articles (16, 84).

It is interesting to note that smoking cessation seems to have a stronger influence on ESSC risk in Western populations than in Asian populations. The incidence rate of ESCC is highest in Asian countries globally, with an estimated 80% of all global ESCC cases occurring in Asia, and China alone contributed to more than half of these cases(85). Despite the much higher prevalence of tobacco smoking in men than women in Asian populations (e.g. 25.5 times higher in men than women in China), the sex difference in the incidence rate of ESCC is less marked (e.g. 2.8 times higher in men than women in China) (86, 87). Thus, the high risk of ESCC in Asian populations is likely to be attributable to other risk factors ,e.g. dietary factors (including hot food and beverage, red and processed meat, low vegetables and fruit, etc.) tobacco smoke pollution, household air pollution, and other sources of polycyclic aromatic hydrocarbons, and genetic factors (88-94). The high baseline ESCC risk posed by risk factors other than tobacco might have neutralized the risk reduction related to smoking cessation in Asian populations. Furthermore, a large proportion of Asian studies did not adjust for confounders, e.g. alcohol consumption, which might have led to an overestimation of the risk of ESCC in former smokers in the study.

In conclusion, this comprehensive systematic review and meta-analysis of 52 studies from different regions globally suggests that smoking cessation is associated with a rapid and strong reduction in the risk of ESCC. The benefits of smoking cessation on ESCC were stronger in Western populations than in Asian populations. Any reduction of EAC risk following smoking cessation is limited and slow. The preventive effects of smoking cessation on esophageal cancer shown in this study can help guide future health policy and clinical practice.

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Notes

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Figure Legends:

Figure 1: Flow chart of study selection. ESCC= esophageal squamous cell carcinoma; EAC= esophageal adenocarcinoma.

Figure 2: Forest plot of risk ratio of esophageal squamous cell carcinoma among former smokers with non-smokers as reference, stratified by study design. The diamonds represent the effect sizes for the studies combined, the squares represent the effect sizes of individual studies and the weights given to the studies, and the error bars represent the corresponding 95% confidence intervals. CI=confidence interval.

Figure 3: Risk ratio of esophageal squamous cell carcinoma and adenocarcinoma by duration since smoking cessation, using current smokers as reference. A) effect sizes for esophageal squamous cell carcinoma; B) effect sizes for esophageal adenocarcinoma. Error bars=95% confidence interval.

Figure 4: Forest plot of risk ratio of esophageal adenocarcinoma among former smokers with non-smokers as reference, stratified by study design. The diamonds represent the effect sizes for the studies combined, the squares represent the effect sizes of individual studies and the weights given to the studies, and the error bars represent the corresponding 95% confidence intervals. CI=confidence interval.

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SUPPLEMENTARY MATERIALS

Tobacco Smoking Cessation and Risk of Esophageal Cancer by Histological Type: Systematic Review and Meta-analysis

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Supplementary Methods

Search Strategies

Medline

1. (esophagus or gastrointestinal tract).sh. or esophageal.tw. or oesophageal.tw. or esophagus.tw. or oesophagus.tw. or upper digestive.tw. or upper aerodigestive.tw. or upper gastrointestin.tw.
2. (neoplasms or carcinoma or carcinoma, squamous cell or adenocarcinoma).sh. or tumour*.ab. or tumor*.ab. or malignan*.ab. or neoplas*.ab. or cancer*.ab. or carcinoma*.ab.
3. esophageal neoplasms.sh.
4. (smoking or smoking cessation or tobacco or "tobacco use cessation").sh. or tobacco*.tw. or smok*.tw. or cigarette*.tw. or risk factor*.tw. or risk factors.sh. or protective factor.sh. or risk assessment.sh. or protective factor*.tw. or risk assessment*.tw.
5. #1 AND #2 OR #3
6. #4 AND #5

Embase

1. 'esophageal' OR 'esophagus' OR 'oesophageal' OR 'oesophagus' OR 'upper gastrointestinal' OR 'upper aerodigestive' OR 'upper digestive'
2. 'neoplasm'/exp OR 'cancer'/exp OR 'carcinoma'/exp OR 'squamous cell carcinoma'/exp OR 'adenocarcinoma'/exp OR 'tumour'/exp OR 'tumor'/exp OR 'malignancy' OR 'neoplasia'/exp
3. 'smoke'/exp OR 'smoking'/exp OR 'smokeless' OR 'smoking cessation'/exp OR 'tobacco'/exp OR 'tobacco use cessation'/exp OR 'tobacco use disorder'/exp OR 'tobacco dependence'/exp OR 'smoking dependence' OR 'nicotine'/exp OR 'nicotine dependence'/exp OR 'cigarette'/exp
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1. TOPIC: (esophageal) *OR* TOPIC: (esophagus) *OR* TOPIC: (oesophageal) *OR* TOPIC: (oesophagus) *OR* TOPIC: (upper gastrointestinal) *OR* TOPIC: (upper aerodigestive) *OR* TOPIC: (upper digestive)
2. TOPIC: (neoplasm) *OR* TOPIC: (cancer) *OR* TOPIC: (carcinoma) *OR* TOPIC: (squamous cell carcinoma) *OR* TOPIC: (adenocarcinoma) *OR* TOPIC: (upper aerodigestive) *OR* TOPIC: (upper digestive) *OR* TOPIC: (tumour) *OR* TOPIC: (tumor) *OR* TOPIC: (malignancy) *OR* TOPIC: (neoplasia)
3. TOPIC: (smoke) *OR* TOPIC: (smoking) *OR* TOPIC: (smokeless) *OR* TOPIC: (smoking cessation) *OR* TOPIC: (tobacco) *OR* TOPIC: (tobacco use cessation) *OR* TOPIC: (tobacco use disorder) *OR* TOPIC: (tobacco dependence) *OR* TOPIC: (smoking dependence) *OR* TOPIC: (nicotine dependence) *OR* TOPIC: (cigarette)
4. #1 AND #2 AND #3

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1. 'esophageal' or 'esophagus' or 'oesophageal' or 'oesophagus' or 'upper gastrointestinal' or 'upper aerodigestive' or 'upper digestive'
2. 'neoplasm' or 'cancer' or 'carcinoma' or 'squamous cell carcinoma' or 'adenocarcinoma' or 'tumour' or 'tumor' or 'malignancy' or 'neoplasia'
3. MeSH descriptor: [Esophageal Neoplasms]
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Supplementary Tables

Supplementary Table 1: Characteristics of included case-control studies for risk ratio of esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC)*

Reference	Country	Study period	Sex	Tumor histology	Cases (n)	Controls (n)	Study design	Case recruitment	Smoking exposure
Steevens et al.2010 (1)	Netherlands	1986-2002	Both	ESCC/EAC	107/145	3962	P	incident	main
Pandeya et al.2008 (2)	Australia	2002-2005	Both	ESCC/EAC	303/367	1580	P	prevalent	main
Hashibe et al.2007 (3)	Europe	2000-2002	Both	ESCC/EAC	192/35	1114	H	incident	main
Vioque et al.2008 (4)	Spain	1995-1999	Both	ESCC	160	455	H	incident	main
De Stefani et al.2005 (5)	Uruguay	1996-2003	Both	ESCC	200	400	H	incident	confounder
Lagergren et al.2000 (6)	Sweden	1995-1997	Both	ESCC/EAC	167/189	820	P	incident	main
Zambon et al.2000 (7)	North Italy	1992-1997	M	ESCC	275	593	H	incident	main
Kabat et al.1993 (8)	US	1981-1990	M,W	ESCC/EAC	214/194	6772	H	incident	main
Gammon et al.1997 (9)	US	1993-1995	Both	ESCC/EAC	221/293	695	P	incident	main
Launoy et al.1997 (10)	France	1991-1994	M	ESCC	208	399	H	incident	main
Tanaka et al.2010 (11)	Japan	2000-2008	Both	ESCC	742	820	H	incident	main
Szymanska et al.2011 (12)	Brazil	1998	Both	ESCC	171	1707	H	incident	main
Castelletto et al.1994 (13)	Argentina	1986-1989	Both	ESCC	131	262	H	incident	main
Bosetti et al.2000 (14)	Italy+Swiss	1992-1999	Both	ESCC	404	1070	H	incident	main
Lee et al.2005 (15)	Taiwan	1996-2003	Both	ESCC	513	818	H	incident	main
Venerito et al.2011 (16)	Germany	2006-2010	Both	ESCC	75	75	H	incident	confounder
Brown et al.1994 (17)	US	1986-1989	M	ESCC	373	1364	P	incident	main
Wang et al.2013 (18)	China	2010-2012	Both	ESCC	866	952	H	incident	confounder
Lindblad et al.2005 (19)	UK	1994-2001	Both	ESCC/EAC	140/287	10000	P	prevalent	main
Wang et al.2007 (20)	China	2004-2006	M	ESCC	355	408	P	incident	main
Shivappa et al.2015 (21)	Iran	NA	Both	ESCC	47	96	H	NA	confounder
Nasrollahzadeh et al.2008 (22)	Iran	2003-2007	Both	ESCC	300	571	P	prevalent	main
Chen et al.2011 (23)	China	2004-2010	Both	ESCC	150	300	H	prevalent	confounder
Wu et al.2006 (24)	Taiwan	NA	M	ESCC	165	255	H	prevalent	main
De Stefani et al.1990 (25)	Uruguay	1985-1988	M,W,Both	ESCC	261	522	H	incident	main
Sewram et al.2003 (26)	Uruguay	1988-2000	Both	ESCC	344	469	H	incident	confounder
Vaughan et al.1995 (27)	US	1983-1990	Both	ESCC/EAC	106/298	724	P	prevalent	main
Gallus et al.2001 (28)	Italy+Swiss	1984-1999	W	ESCC	114	425	H	incident	main
Gao et al.2011 (29)	China	1997-2005	M	ESCC	376	1107	P	incident	main
Mota et al.2013 (30)	Brazil	1998-2003	Both	ESCC	99	223	H	NA	main

Gledovic et al.2007 (31)	Serbia	1998-2002	Both	ESCC	102	102	H	incident	main
Morita et al.2003 (32)	Japan	1989-1998	M	ESCC	88	228	H	prevalent	main
Sharp et al.2001 (33)	UK	1993-1996	W	ESCC	159	159	P	incident	main
Kollarova et al.2013 (34)	Czech	2000-2002	Both	ESCC/EAC	48/34	200	H	incident	main
Lee et al.2009 (35)	Europe	1987-2005	Both	ESCC	152	2221	H	incident	main
Lee et al.2012 (36)	Taiwan	2001-2007	Both	ESCC	305	2250	H	incident	confounder
Wu et al.2001 (37)	US	1992-1997	Both	EAC	222	1356	P	prevalent	main
Brown et al.1994 (38)	US	1986-1990	M	EAC	174	750	P	incident	main
Anderson et al.2007 (39)	Ireland	2002-2004	Both	EAC	227	260	P	NA	main
Victora et al.1987 (40)	Brazil	1985-1986	M,W,Both	ESCC	171	342	H	incident	main
Cheng et al.2000 (41)	UK	1993-1996	W	EAC	74	74	P	prevalent	main
Xu et al.2013 (42)	US	2003-2004	Both	EAC	218	218	P	prevalent	confounder
Bradbury et al.2009 (43)	US	1999-2005	Both	EAC	313	455	H	incident	confounder
De Jonge et al.2006 (44)	Netherlands	2003-2005	Both	EAC	91	244	H	incident	main

*H=hospital-based study; M=men; P=population-based study; W=women.

Supplementary Table 2: Characteristics for included cohort studies for risk ratio of esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC)*

Reference	Country	Study period	Sex	Tumor histology	Baseline age	Cases (n)	Cohort members(n)	Follow-up (year)	Smoking exposure	Outcome assessment
Freedman et al.2007 (45)	US	1995-1996	Both	ESCC/EAC	63	302	474606	4.6	main	Record linkage
Zendehdel et al.2008 (46)	Sweden	1971-1993	M	ESCC/EAC	35	366	336381	22.2	main	Record linkage
Ishiguro et al.2009 (47)	Japan	1990-1994	M	ESCC	40-59	215	44970	11- 14	main	Record linkage
Bodelon et al.2011 (48)	US	1993-1998	W	ESCC/EAC	50-79	57	161086	11-16	confounder	Self-report
Ramus et al.2012 (49)	UK	1996-2003	M,W, Both	EAC	64	73	956	3.8	main	Record linkage
Yates et al.2014 (50)	UK	1993-1997	Both	EAC	67	66	24068	11-15	main	Record linkage
Sikkema et al.2011 (51)	Nether-lands	2003-2004	Both	EAC	61	26	713	4	main	Record linkage
Coleman et al.2012 (52)	Ireland	1993-2008	Both	EAC	62	80	3167	7.5	main	Record linkage

*M=men; W=women.

Supplementary Table 3: Adjusted variables and quality scores of included studies for risk ratio of esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC)

Reference	Variables adjusted for*									NOS-ESCC	NOS-EAC
	Age	Sex	Alcohol	BMI	Reflux	Diet	Race	SES	Location		
Case-control studies											
Steevens et al.2010 (1)	1	1	1	1	0	1	0	1	0	9	8
Pandeya et al.2008 (2)	1	1	1	1	1	0	0	1	1	6	7
Hashibe et al.2007 (3)	1	1	1	1	0	1	0	1	1	7	7
Vioque et al.2008 (4)	1	1	1	0	0	1	0	1	1	9	/
De Stefani et al.2005 (5)	1	1	0	0	0	0	0	0	0	8	/
Lagergren et al.2000 (6)	1	1	1	1	1	1	0	1	0	9	9
Zambon et al.2000 (7)	1	1	1	0	0	0	0	1	1	7	/
Kabat et al.1993 (8)	1	1	1	0	0	0	1	1	1	6	6
Gammon et al.1997 (9)	1	1	1	1	0	0	1	1	1	9	9
Launoy et al.1997 (10)	1	1	1	0	0	0	0	1	1	7	/
Tanaka et al.2010 (11)	1	1	1	0	0	0	0	0	1	6	/
Szymanska et al.2011 (12)	1	1	1	0	0	1	0	1	1	9	/
Castelletto et al.1994 (13)	1	1	1	0	0	0	0	1	1	7	/
Bosetti et al.2000 (14)	1	1	1	0	0	0	0	1	1	7	/
Lee et al.2005 (15)	1	1	1	0	0	1	0	1	1	7	/
Venerito et al.2011 (16)	1	1	0	0	0	0	0	0	0	4	/
Brown et al.1994 (17)	1	1	1	0	0	0	0	1	1	8	/
Wang et al.2013 (18)	1	1	0	0	0	0	0	0	0	4	/
Lindblad et al.2005 (19)	1	1	1	1	1	0	0	0	0	9	9
Wang et al.2007 (20)	1	1	0	0	0	0	0	1	1	7	/
Shivappa et al.2015 (21)	1	1	0	0	0	0	0	0	0	3	/
Nasrollahzadeh et al.2008 (22)	1	1	0	0	0	0	1	1	1	6	/
Chen et al.2011 (23)	1	1	0	0	0	0	0	0	0	4	/
Wu et al.2006 (24)	1	1	1	0	0	0	0	1	0	6	/
De Stefani et al.1990 (25)	1	1	0	0	0	0	0	0	0	6	/
Sewram et al.2003 (26)	1	1	0	0	0	0	0	0	0	6	/
Vaughan et al.1995	1	1	1	1	0	0	1	1	0	9	8

(27)											
Gallus et al.2001 (28)	1	1	1	1	0	1	0	1	1	7	/
Gao et al.2011 (29)	1	1	0	0	0	0	0	0	1	7	/
Mota et al.2013 (30)	1	1	0	0	0	0	0	0	1	4	/
Gledovic et al.2007 (31)	1	1	0	0	0	0	0	0	1	4	/
Morita et al.2003 (32)	1	1	0	0	0	0	0	0	1	5	/
Sharp et al.2001 (33)	1	1	0	0	0	1	0	0	0	8	/
Kollarova et al.2013 (34)	1	1	1	1	0	1	0	0	0	6	6
Lee et al.2009 (35)	1	1	1	0	0	0	0	1	1	6	/
Lee et al.2012 (36)	1	1	0	0	0	0	0	0	1	5	/
Wu et al.2001 (37)	1	1	0	0	0	0	1	1	1	/	8
Brown et al.1994 (38)	1	1	1	0	0	0	0	1	0	/	6
Anderson et al.2007 (39)	1	1	1	1	1	0	0	1	1	/	8
Victora et al.1987 (40)	1	1	0	0	0	0	0	0	1	8	/
Cheng et al.2000 (41)	1	1	0	0	0	0	0	0	0	/	8
Xu et al.2013 (42)	1	1	0	0	0	0	1	0	0	/	5
Bradbury et al.2009 (43)	1	1	0	0	0	0	0	0	0	/	3
De Jonge et al.2006 (44)	1	1	1	1	1	0	0	1	0	/	7
Cohort studies											
Freedman et al.2007 (45)	1	1	1	1	0	1	0	1	0	8	7
Zendehdel et al.2008 (46)	1	1	0	1	0	0	0	0	1	6	7
Ishiguro et al.2009 (47)	1	1	1	1	0	1	0	0	1	8	/
Bodelon et al.2011 (48)	1	1	1	0	0	0	0	0	1	5	7
Ramus et al.2012 (49)	0	0	0	0	0	0	0	0	0	/	6
Yates et al.2014 (50)	1	1	0	0	0	0	0	0	0	/	7
Sikkema et al.2011 (51)	1	1	0	0	0	0	0	0	0	/	6
Coleman et al.2012 (52)	1	1	0	0	1	0	0	1	0	/	9

* For the adjusted variables, 1 represents adjusted that variable, 0 represents unadjusted that variable. Abbreviation: BMI=Body mass index; EAC=esophageal adenocarcinoma; ESCC= esophageal squamous cell carcinoma; NOS=Newcastle-Ottawa; SES=socio-economic status.

Supplementary Table 4: Quality assessment for each item of included case-control studies for risk ratio of esophageal squamous cell carcinoma and adenocarcinoma*

Reference	1. Case definition	2. Representative-ness of cases	3. Selection of controls	4. Definition of controls	5. Adjustment for alcohol/BMI †	6. Adjustment for diet/reflux‡	7. Ascertainment of the exposure	8. Method of ascertainment	9. Non-response rate	10. Smoking as main exposure	Total score
Case-control studies for esophageal squamous cell carcinoma											
Steevens et al.2010 (1)	1	1	1	1	1	1	0	1	1	1	9
Pandeya et al.2008 (2)	1	1	1	0	1	0	0	1	0	1	6
Hashibe et al.2007 (3)	1	0	0	1	1	1	0	1	1	1	7
Vioque et al.2008 (4)	1	1	0	1	1	1	1	1	1	1	9
De Stefani et al.2005 (5)	1	1	0	1	1	1	1	1	1	0	8
Lagergren et al.2000 (6)	1	1	1	0	1	1	1	1	1	1	9
Zambon et al.2000 (7)	1	1	0	1	1	0	0	1	1	1	7
Kabat et al.1993 (8)	1	0	0	1	1	0	1	1	0	1	6
Gammon et al.1997 (9)	1	1	1	1	1	0	1	1	1	1	9
Launoy et al.1997 (10)	1	1	0	1	1	0	1	1	0	1	7
Tanaka et al.2010 (11)	1	1	0	1	1	0	0	1	0	1	6
Szymanska et al.2011 (12)	1	1	0	1	1	1	1	1	1	1	9
Castelletto et al.1994 (13)	1	1	0	1	1	0	1	1	0	1	7
Bosetti et al.2000 (14)	1	1	0	1	1	0	1	1	0	1	7
Lee et al.2005 (15)	1	1	0	1	1	1	0	1	0	1	7
Venerito et al.2011 (16)	1	0	0	1	0	0	0	1	1	0	4
Brown et al.1994 (17)	1	1	1	0	1	0	1	1	1	1	8
Wang et al.2013 (18)	1	1	0	0	0	0	1	1	0	0	4
Lindblad et al.2005 (19)	0	1	1	1	1	1	1	1	1	1	9
Wang et al.2007 (20)	1	1	1	1	0	0	1	1	0	1	7

Shivappa et al.2015 (21)	1	0	0	1	0	0	0	1	0	0	3
Nasrollahzadeh et al.2008 (22)	1	1	1	1	0	0	0	1	0	1	6
Chen et al.2011 (23)	1	0	0	1	0	0	1	1	0	0	4
Wu et al.2006 (24)	0	0	0	1	1	1	0	1	1	1	6
De Stefani et al.1990 (25)	1	1	0	1	0	0	0	1	1	1	6
Sewram et al.2003 (26)	1	1	0	1	0	0	1	1	1	0	6
Vaughan et al.1995 (27)	1	1	1	1	1	1	0	1	1	1	9
Gallus et al.2001 (28)	1	0	0	1	1	1	1	1	0	1	7
Gao et al.2011 (29)	1	1	1	1	0	0	0	1	1	1	7
Mota et al.2013 (30)	1	0	0	1	0	0	0	1	0	1	4
Gledovic et al.2007 (31)	1	1	0	0	0	0	0	1	0	1	4
Morita et al.2003 (32)	1	1	0	1	0	0	0	1	0	1	5
Sharp et al.2001 (33)	1	1	1	1	0	1	0	1	1	1	8
Kollarova et al.2013 (34)	1	1	0	1	1	0	0	1	0	1	6
Lee et al.2009 (35)	1	1	0	1	1	0	0	1	0	1	6
Lee et al.2012 (36)	1	1	0	1	0	0	0	1	1	0	5
Victora et al.1987 (40)	1	1	0	1	1	1	1	1	0	1	8
Case-control studies for esophageal adenocarcinoma											
Steevens et al.2010 (1)	1	1	1	1	1	0	0	1	1	1	8
Wu et al.2001 (37)	1	1	1	1	0	0	1	1	1	1	8
Brown et al.1994 (38)	1	1	1	0	0	0	0	1	1	1	6
Pandeya et al.2008 (2)	1	1	1	0	1	1	0	1	0	1	7
Hashibe et al.2007 (3)	1	0	0	1	1	0	1	1	1	1	7
Anderson et al.2007 (39)	1	1	1	1	1	1	0	1	0	1	8
Lagergren et al.2000 (6)	1	1	1	0	1	1	1	1	1	1	9
Kabat et al.1993 (8)	1	1	0	1	0	0	0	1	1	1	6
Gammon et al.1997 (9)	1	1	1	1	1	0	1	1	1	1	9
Cheng et al.2000 (41)	1	1	1	1	0	0	1	1	1	1	8

Xu et al.2013 (42)	1	1	1	1	0	0	0	1	0	0	5
Lindblad et al.2005 (19)	0	1	1	1	1	1	1	1	1	1	9
Bradbury et al.2009 (43)	1	0	0	0	0	0	0	1	1	0	3
Vaughan et al.1995 (27)	1	1	1	1	1	0	0	1	1	1	8
De Jonge et al.2006 (44)	1	1	0	1	1	1	0	1	0	1	7
Kollarova et al.2013 (34)	1	1	0	1	1	0	0	1	0	1	6

* BMI=body mass index.

† Adjustment for alcohol in studies for esophageal squamous cell carcinoma; adjustment for BMI in studies for esophageal adenocarcinoma.

‡ Adjustment for diet in studies for esophageal squamous cell carcinoma; adjustment for reflux in studies for esophageal adenocarcinoma.

Supplementary Table 5: Quality assessment for each item of included cohort studies for risk ratio of esophageal squamous cell carcinoma and adenocarcinoma*

Reference	1. Representativeness of exposed cohort	2. Selection of non-exposed cohort	3. Ascertainment of the exposure	4. Exclusion of outcome at baseline	5. Adjustment for alcohol/BMI †	6. Adjustment for diet/reflux‡	7. Assessment of the outcome	8. Follow-up for at least 10 years	9. Loss to follow-up <20%	10. Smoking as main exposure	Total score
Cohort studies for esophageal squamous cell carcinoma											
Freedman et al.2007 (45)	1	1	0	1	1	1	1	0	1	1	8
Zendehdel et al.2008 (46)	0	1	0	1	0	0	1	1	1	1	6
Ishiguro et al.2009 (47)	1	1	0	0	1	1	1	1	1	1	8
Bodelon et al.2011 (48)	0	1	0	1	0	0	1	1	1	0	5
Cohort studies for esophageal adenocarcinoma											
Freedman et al.2007 (45)	1	1	0	1	1	0	1	0	1	1	7
Zendehdel et al.2008 (46)	0	1	0	1	1	0	1	1	1	1	7
Ramus et al.2012 (49)	1	1	0	1	0	0	1	0	1	1	6
Yates et al.2014 (50)	1	1	0	1	0	0	1	1	1	1	7
Bodelon et al.2011 (48)	0	1	0	1	1	1	1	1	1	0	7
Sikkema et al.2011 (51)	1	1	0	1	0	0	1	0	1	1	6
Coleman et al.2012 (52)	1	1	1	1	0	1	1	1	1	1	9

* BMI=body mass index.
† Adjustment for alcohol in studies for esophageal squamous cell carcinoma; adjustment for BMI in studies for esophageal adenocarcinoma.
‡ Adjustment for diet in studies for esophageal squamous cell carcinoma; adjustment for reflux in studies for esophageal adenocarcinoma.

Supplementary Table 6: Studies reporting the association between smoking cessation and risk of esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma (EAC) by cessation latency*

Reference	Study design	Histology	Reference group	No. of cases	No. of controls/ cohort	Risk ratios (95% confidence interval) by duration since quitting smoking
Steevens et al.2010 (1)	Case-control	ESCC	NS	107	3962	<10y:1.42 (0.62-3.23); 10-20y:1.28 (0.58-2.84); >20y:1.46 (0.63-3.42)
Pandeya et al.2008 (2)	Case-control	ESCC	NS	303	1580	⩽10y:2.39 (1.42-4.01); 10.01-20y:2.94 (1.77-4.89); 20.01-30y:2.20 (1.32-3.66); >30y:1.44 (0.82-2.52)
Hashibe et al.2007 (3)	Case-control	ESCC	CS	192	1114	2-4y:0.32 (0.09-1.18); 5-9y:0.89 (0.4-1.96); 10-19y:0.30 (0.13-0.72); >20y:0.16 (0.07-0.39)
Vioque et al.2008 (4)	Case-control	ESCC	CS	160	455	<10y:0.44 (0.20 -0.96); ⩾ 10y:0.49 (0.23-1.06)
De Stefani et al.2005 (5)	Case-control	ESCC	NS	200	400	1-9y:2.7(1.4-4.9); 10-19y:1.4(0.7-2.9); ⩾20y,1.6(0.8-3.2)
Lagergren et al.2000 (6)	Case-control	ESCC	CS	167	820	<5y:0.456 (0.173-1.204); 5-9y: 0.433 (0.0.172-1.089); 10-19y:0.291 (0.134-0.63);⩾20y:0.155 (0.08-0.3)
Zambon et al.2000 (7)	Case-control	ESCC	NS	275	593	<5y:7.70 (3.21-18.49); 5-9y:4.10(1.84-9.10); ⩾10y:1.54 (0.79-3.02)
Kabat et al.1993 (8)	Case-control	ESCC	CS	214	6772	in men: 1-5y:0.5 (0.3-1.0); 6-10y:0.4 (0.2-0.8); 11-20y:0.3 (0.2-0.6); >21y:0.2 (0.1-0.3); in women:1-10y: 0.4 (0.2- 0.9); >11y:0.3 (0.1-0.5)
Gammon et al.1997 (9)	Case-control	ESCC	NS	221	695	<11y:5.6(2.9-10.8); 11-20y:2.3(1.1-4.8); 21-30y:1.0(0.4-2.7); >30y:1.8(0.8-4.2)
Launoy et al.1997 (10)	Case-control	ESCC	CS	208	399	1-5y:1.43 (0.77-2.64); 6-10y:0.69 (0.33-1.46); ⩾11y:0.51 (0.26-1.00)
Tanaka et al.2010 (11)	Case-control	ESCC	NS	742	820	<1y:21.8 (5.7- 82.9); 1-2y:3.7 (1.2– 11.5); 3-9y:4.6 (2.1- 10.1); >10y:2.8 (1.4– 5.4)
Szymanska et al.2011 (12)	Case-control	ESCC	CS	171	1707	2-4y:0.42 (0.18-0.99); 5-9y:0.32 (0.13-0.81); 10-19y:0.45(0.23-0.89); ⩾20y:0.23 (0.11-0.49)
Castelletto et al.1994 (13)	Case-control	ESCC	CS	131	262	2-7y: 1.5(0.6-3.3); 8-19y:0.5 (0.2-1.2); ⩾20y:1.3(0.5-3.3)
Bosetti et al.2000 (14)	Case-control	ESCC	CS	404	1070	1-2y: 1.37 (0.64-2.96); 3-5y:1.10 (0.60-2.04); 6-9y:0.58 (0.31-1.07); 10-14y:0.31 (0.17-0.56); ⩾15y:0.31 (0.20-0.49)
Lee et al.2005 (15)	Case-control	ESCC	CS	513	818	1-5y:1.4 (0.8-2.3); 6-10y:0.4 (0.2-0.9); >10y:0.5 (0.3-0.9)
Victora et al.1987 (40)	Case-control	ESCC	CS	171	342	all:1-7y:1.00(0.72-1.39); 8-19y:0.39(0.20-0.78); >20y:0.48(0.25-0.90); in men:1-7y:1.01(0.71-1.42); 8-19y:0.38(0.18-0.79);>20y:0.45(0.23-0.88); in women: 1-7y:0.94(0.32-2.83); 8-19y:0.40(0.07-2.39); >20y:0.94(0.12-7.27)
Freedman et al.2007 (45)	Cohort	ESCC	NS	97	474606	1-4y:10.30 (3.88 -27.35); 5-9y:6.70 (2.57-17.47); >10y:3.24(1.40-7.49)

Zendehdel et al.2008 (46)	Cohort	ESCC	NS	236	336381	<5y:1.0 (0.3-3.5); ⩾5y:0.8 (0.3-2.1)
Steevens et al.2010 (1)	Case-control	EAC	NS	145	3962	<10y:1.66 (0.95 -2.91); 10-20y:1.42 (0.80 -2.51); >20y:1.32 (0.70-2.47)
Wu et al.2001 (37)	Case-control	EAC	NS	222	1356	1-5y:2.17(1.2-3.9); 6-10y:1.09(0.5-2.3); 11-19y:1.74(1.1-2.9); >20y:1.33(0.8-2.1)
Brown et al.1994 (38)	Case-control	EAC	NS	174	750	1-9y:2.0 (1.0-4.1); 10-19y:2.4 (1.2-4.9); 20-29y:2.2 (1.0-4.7);>30y: 3.1 (1.5-6.6)
Pandeya et al.2008 (2)	Case-control	EAC	NS	367	1580	⩽10y:1.58 (1.00-2.51); 10.01-20y:1.99 (1.29-3.06); 20.01-30y: 1.26(0.79-1.99);>30y:1.06 (0.65-1.73)
Hashibe et al.2007 (3)	Case-control	EAC	CS	35	1114	2-4y:1.38 (0.26-7.30); 5-9y:1.19 (0.24-5.81);); 10-19y:0.60 (0.12-3.03); >20y:1.19 (0.39-3.61)
Anderson et al.2007 (39)	Case-control	EAC	NS	227	260	< 26y:4.89 (2.74-8.71); 26-41y:2.51 (1.30 - 4.83); > 41y:1.40 (0.74-2.66)
Lagergren et al.2000 (6)	Case-control	EAC	CS	189	820	<5y:1.872(0.728-4.848); 5-9y: 0.864 (0.307-2.426); 10-19y: 1.012 (0.495-2.068); ⩾20y: 0.949 (0.526-1.712)
Kabat et al.1993 (8)	Case-control	EAC	CS	194	6772	in men:1-5y:0.5 (0.2-1.1);6-10y:1.1 (0.6-1.9);11-20y:1.2 (0.8-1.9); >21y:0.5 (0.3-0.9); in women:1-10y:0.3 (0.1-1.7); >11y:0.3 (0.1-1.7)
Gammon et al.1997 (9)	Case-control	EAC	NS	293	695	<11y:2.7(1.6-4.4); 11-20y:2.3(1.4-3.8); 21-30y:1.9(1.1-3.2); >30y:1.2(0.7-2.2)
Freedman et al.2007 (45)	Cohort	EAC	NS	205	474606	1-4y:2.21 (0.99-4.93); 5-9y:4.04 (2.33-7.00); >10y:2.67 (1.72 -4.16)
Zendehdel et al.2008 (46)	Cohort	EAC	NS	130	336381	<5y:2.1 (0.9-4.9); ⩾5y:0.8 (0.3-1.8)
Ramus et al.2012 (49)	Cohort	EAC	NS	73	956	all: <10y:1.98 (0.9-4.4); ⩾10y:3.22 (1.6-6.5); in men: <10y:2.52 (0.94-6.8); ⩾10y:4.15 (1.7-10.1); in women: <10y:1.14 (0.24-5.5); ⩾10y:1.8 (0.5-6.8)

* CS=current smoker; NS=non-smoker.

Supplementary Table 7: Smoking cessation and the risk of esophageal squamous cell carcinoma and esophageal adenocarcinoma by cessation latency

Type of analysis	Esophageal squamous cell carcinoma					Esophageal adenocarcinoma				
	Smoking status	RR (95% CI)	Studies (n)	$P_{Heterogeneity}$*	I^2(%)	Smoking status	RR (95% CI)	Studies (n)	$P_{Heterogeneity}$*	I^2(%)
Pooled with all data available†										
	Current smokers	Reference				Current smokers	Reference			
	Quit<5 years ago	0.96(0.73-1.25)	12	.04	45.5	Quit<5 years ago	0.81(0.52-1.26)	5	.26	23.5
	Quit 5-9 years ago	0.59(0.47-0.75)	10	.44	0.0	Quit 5-9 years ago	0.87(0.58-1.30)	5	.23	28.2
	Quit 10-20 years ago	0.42(0.34-0.51)	11	.62	0.0	Quit 10-20 years ago	0.95(0.78-1.15)	8	.47	0.0
	Quit >20 years ago	0.34(0.25-0.47)	11	.001	65.8	Quit >20 years ago	0.72(0.52-1.01)	8	.003	67.0
	Non-smokers	0.22(0.18-0.28)	15	.002	59.3	Non-smokers	0.40(0.33-0.48)	12	.15	29.9
Pooled with data from those studies reporting all quit-smoking duration categories										
	Current smokers	Reference				Current smokers	Reference			
	Quit <5 years ago	0.58(0.34-0.99)	5	.05	58.3	Quit <5 years ago	0.90(0.51-1.57)	4	.21	34.6
	Quit 5-9 years ago	0.51(0.36-0.71)	5	.46	0.0	Quit 5-9 years ago	0.78(0.45-1.36)	4	.19	36.7
	Quit 10-20 years ago	0.33(0.24-0.44)	5	.89	0.0	Quit 10-20 years ago	0.90(0.62-1.30)	4	.25	27.3
	Quit >20 years ago	0.22(0.17-0.29)	5	.41	0.0	Quit >20 years ago	0.64(0.43-0.97)	4	.17	40.6
	Non-smokers	0.18(0.13-0.24)	5	.21	32.5	Non-smokers	0.44(0.33-0.57)	4	.54	0.0

*P values from two-sided Cochran's Q test. CI=confidence interval; RR=risk ratio.
†One study (Tanaka et al.2010) reported data for 0-1 and 1-2 years of smoking cessation, we pooled them into <5 years group and we also pooled 3-9 years group into 5-9 years group. Two studies (Castelletto et al.1994 and Victora at al.1987) reported data for 1-7 years and they were reclassified into <5 years group, and data of 8-19 years and 10-14 years were reclassified into 10-20 years. And one study (Bosetti et al.2000) had >15 years group which was put into >20 years group in our analysis.

Supplementary Table 8: Tobacco smoking status and risk of esophageal adenocarcinoma, using non-smokers as reference

	Former smokers				Current smokers			
Study characteristics	**Risk ratio (95% CI)**	**Studies (n)**	$P_{heterogeneity}$*	I^2 (%)†	**Risk ratio (95% CI)**	**Studies (n)**	$P_{heterogeneity}$*	I^2 (%)†
Overall	1.66 (1.48-1.85)	23	.30	11.6	2.35 (2.04-2.69)	23	.13	26.0
Study design								
Case-control	1.65 (1.47-1.86)	17	.39	5.1	2.24 (1.91-2.64)	17	.09	33.2
Cohort	1.70 (1.23-2.35)	6	.18	34.9	2.65 (2.03-3.46)	6	.53	0.0
Publication year								
⩽1999	1.92 (1.55-2.38)	5	.41	0.0	2.31 (1.84-2.89)	5	.58	0.0
2000-2009	1.62 (1.35-1.96)	11	.10	37.3	2.48 (1.94-3.18)	11	.01	57.0
⩾2010	1.55 (1.23-1.96)	7	.84	0.0	1.99 (1.53-2.58)	7	.87	0.0
Geographic origin								
North America	1.87 (1.62-2.16)	10	.42	2.5	2.52 (2.14-2.96)	10	.82	0.0
Europe	1.48 (1.25-1.76)	12	.47	0.0	2.16 (1.67-2.79)	12	.04	46.1
Oceania	1.46 (1.05-2.02)	1	1.00	0.0	2.51 (1.66-3.82)	1	1.00	0.0
Sex‡								
Men	1.59 (0.96-2.64)	4	.02	71.3	2.12 (1.46-3.07)	4	.06	58.8
Women	1.36 (0.90-2.07)	4	.58	0.0	2.15 (1.27-3.65)	4	.34	9.9
Unspecified	1.65 (1.46-1.86)	16	.39	5.5	2.37 (2.03-2.77)	16	.07	34.8
Response rate								
⩾80%	1.48 (1.23-1.79)	8	.71	0.0	2.08 (1.67-2.60)	8	.28	18.9
<80%	1.83 (1.51-2.20)	10	.10	38.9	2.48 (1.98-3.09)	10	.11	37.2
Unknown	1.61 (1.23-2.11)	5	.58	0.0	2.26 (1.72-2.98)	5	.39	2.4
Smoking exposure								
Main exposure	1.67 (1.46-1.91)	20	.17	23.2	2.33 (1.98-2.73)	20	.06	35.5
Confounder	1.69 (1.31-2.20)	3	.94	0.0	2.21 (1.60-3.06)	3	.89	0.0
Tobacco types								
Cigarettes	1.73 (1.42-2.10)	11	.14	32.6	2.29 (1.93-2.72)	11	.50	0.0

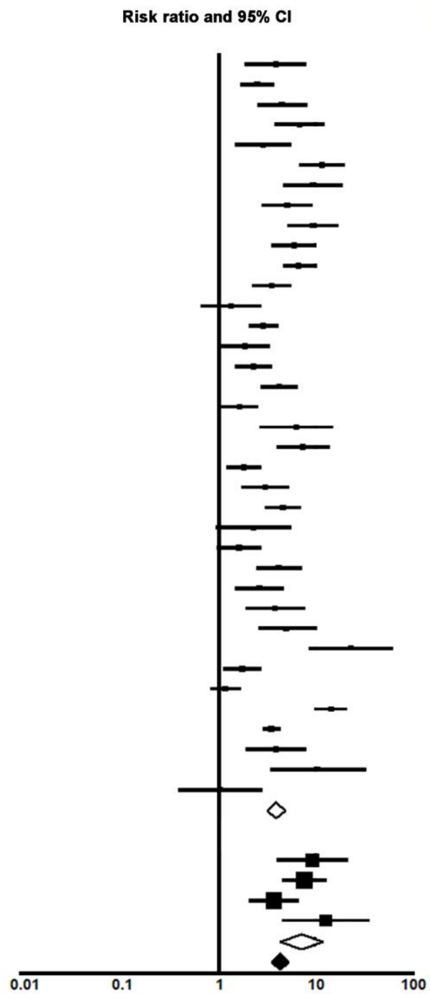
Unspecified	1.62 (1.40-1.88)	12	.56	0.0	2.35 (1.87-2.95)	12	.04	46.2
Study quality								
Low (score<7)	1.85 (1.51-2.27)	7	.49	0.0	2.24 (1.77-2.83)	7	.62	0.0
High (score⩾7)	1.61 (1.41-1.85)	16	.25	17.8	2.34 (1.95-2.79)	16	.05	40.7
Adjusted variables								
Body mass index								
Yes	1.71 (1.45-2.03)	13	.18	25.8	2.43 (1.91-3.11)	12	.01	53.5
No	1.64 (1.39-1.92)	10	.48	0.0	2.27 (1.92-2.69)	11	.81	0.0
Gastroesophageal reflux								
Yes	1.53 (1.24-1.89)	6	.37	8.0	1.97 (1.50-2.58)	6	.20	31.0
No	1.73 (1.51-1.98)	17	.31	12.5	2.46 (2.12-2.84)	17	.33	10.6
Socio- economy								
Yes	1.77 (1.55-2.01)	13	.66	0.0	2.50 (2.08-3.00)	13	.17	27.4
No	1.52 (1.21-1.90)	10	.14	33.0	2.04 (1.69-2.46)	10	.35	10.1
Place of residence								
Yes	1.67 (1.42-1.97)	9	.88	0.0	2.74 (2.28-3.30)	9	.58	0.0
No	1.68 (1.40-2.01)	14	.07	38.5	2.04 (1.72-2.41)	14	.24	20.0
Case-control study								
Study design								
Population-based	1.59 (1.37-1.84)	11	.23	22.8	2.12 (1.73-2.60)	11	.04	48.1
Hospital-based	1.90 (1.48-2.44)	6	.81	0.0	2.62 (1.99-3.47)	6	.76	0.0
Cases recruitment								
Incident	1.93 (1.64-2.28)	10	.75	0.0	2.16 (1.79-2.61)	10	.62	0.0
Prevalent	1.41 (1.20-1.66)	7	.71	0.0	2.11 (1.70-2.61)	7	.17	33.9
Unknown	1.72 (1.06-2.81)	1	1.00	0.0	4.84 (2.72-8.61)	1	1.00	0.0
Cohort study								
Study design								
Population-based	1.96 (1.14-3.35)	3	.10	57.5	2.92 (1.86-4.59)	3	.34	6.6
BE-based	1.51 (0.92-2.49)	2	.56	0.0	2.07 (1.26-3.39)	2	.43	0.0
Occupation-based	1.20 (0.60-2.40)	1	1.00	0.0	2.90 (1.80-4.80)	1	1.00	0.0
Follow-up time								

<10 years	1.98 (1.22-3.22)	3	.15	47.0	2.61 (1.62-4.20)	3	.21	36.5
⩾10 years	1.35 (0.91-2.02)	3	.68	0.0	2.55 (1.70-3.83)	3	.63	0.0
Outcome assessment								
Record linkage	1.65 (1.13-2.41)	5	.11	47.7	2.65 (2.00-3.49)	5	.39	3.2
Self-reported	1.92 (0.79-4.65)	1	1.00	0.0	2.49 (0.52-11.98)	1	1.00	0.0

* P-values from two-sided Cochran's Q test**.** CI=confidence interval.
† I^2 statistics indicating the percentage of variation across studies that is due to heterogeneity.
‡ One study (Ramus et al.2012) reported risk ratio for men and women separately and combined; one study (Kabat et al.1993) reported risk ratio for men and women separately.

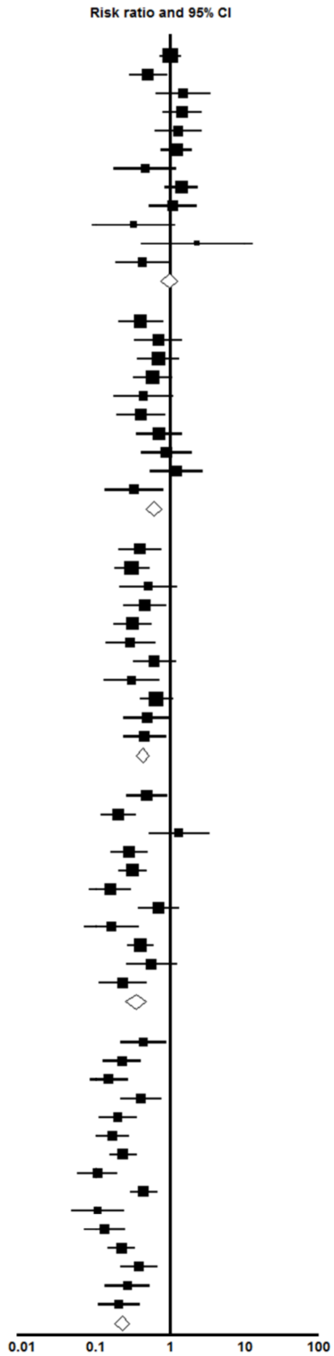
Supplementary Figures

Study	Risk ratio	Lower limit	Upper limit	Relative weight
Case-control				
Victora et al.1987 (40)	3.87	1.88	7.97	2.46
De Stefani et al.1990 (25)	2.49	1.67	3.69	3.02
Kabat et al.1993M (8)	4.50	2.50	8.10	2.70
Kabat et al.1993F (8)	6.80	3.76	12.30	2.70
Castelletto et al.1994 (13)	2.90	1.50	5.60	2.58
Brown et al.1994 (17)	11.57	6.73	19.87	2.79
Vaughan et al.1995 (27)	9.37	4.68	18.75	2.51
Gammon et al.1997 (9)	5.10	2.81	9.24	2.69
Lagergren et al.2000 (6)	9.30	5.09	16.98	2.68
Zambon et al.2000 (7)	6.00	3.55	10.15	2.81
Bosetti et al.2000 (14)	6.66	4.64	9.55	3.08
Gallus et al.2001 (28)	3.54	2.25	5.56	2.94
Sharp et al.2001 (33)	1.34	0.66	2.71	2.49
Sewram et al.2003 (26)	2.88	2.04	4.06	3.10
Morita et al.2003 (32)	1.88	1.05	3.34	2.72
De Stefani et al.2005 (5)	2.30	1.49	3.53	2.97
Lee et al.2005 (15)	4.20	2.75	6.42	2.98
Lindblad et al.2005 (19)	1.64	1.05	2.56	2.95
Wu et al.2006 (24)	6.30	2.69	14.77	2.23
Hashibe et al.2007 (3)	7.41	3.98	13.79	2.64
Wang et al.2007 (20)	1.82	1.21	2.72	3.01
Gledovic et al.2007 (31)	3.00	1.72	5.25	2.76
Pandeya et al.2008 (2)	4.58	2.99	7.02	2.98
Vioque et al.2008 (4)	2.28	0.95	5.49	2.18
Nasrollahzadeh et al.2008 (22)	1.63	0.97	2.75	2.82
Lee et al.2009 (35)	4.17	2.45	7.10	2.80
Steevens et al.2010 (1)	2.63	1.47	4.70	2.72
Tanaka et al.2010 (11)	3.80	1.89	7.65	2.50
Szymanska et al.2011 (12)	4.98	2.59	9.57	2.59
Venerito et al.2011 (16)	23.20	8.60	62.57	1.99
Chen et al.2011 (23)	1.75	1.12	2.73	2.95
Gao et al.2011 (29)	1.17	0.82	1.67	3.08
Lee et al.2012 (36)	14.44	10.01	20.83	3.07
Wang et al.2013 (18)	3.49	2.84	4.29	3.26
Mota et al.2013 (30)	3.88	1.90	7.90	2.48
Kollarova et al.2013 (34)	10.64	3.46	32.72	1.78
Shivappa et al.2015 (21)	1.04	0.39	2.82	1.98
Subtotal	3.81	3.06	4.74	
Cohort				
Freedman et al.2007 (45)	9.27	4.04	21.28	21.24
Zendehdel et al.2008 (46)	7.60	4.52	12.77	32.37
Ishiguro et al.2009 (47)	3.69	2.07	6.58	29.94
Bodelon et al.2011 (48)	12.67	4.55	35.28	16.44
Subtotal	6.95	4.17	11.57	
Overall	4.18	3.42	5.12	



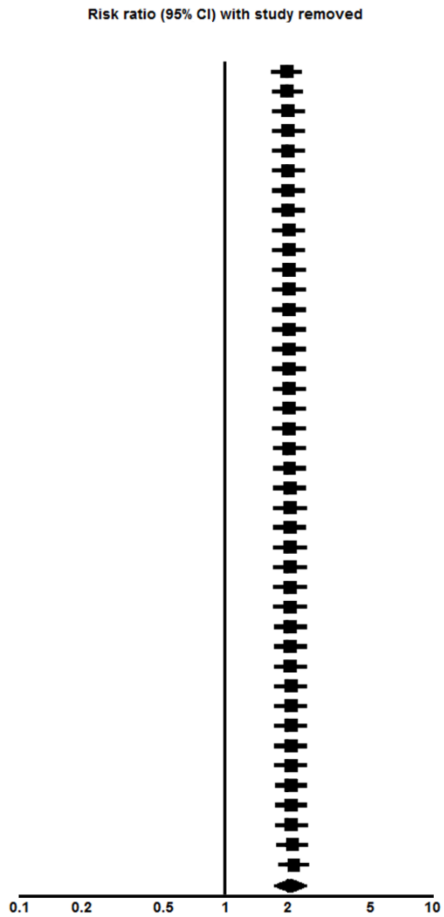
Supplementary Figure 1: Forest plot of risk ratio of esophageal squamous cell carcinoma among current smokers with non-smokers as reference, stratified by study design. The diamonds represent the effect sizes for the studies combined, the squares represent the effect sizes of individual studies and the weights given to the studies, and the error bars represent the corresponding 95% confidence intervals. CI=confidence interval.

Smoking cessation	Risk ratio	Lower limit	Upper limit	Relative weight
<5 years				
Victora et al.1987 (40)	1.00	0.72	1.39	15.69
Kabat et al.1993M (8)	0.50	0.27	0.91	10.09
Castelletto et al.1994 (13)	1.50	0.64	3.52	6.68
Launoy et al.1997 (10)	1.43	0.77	2.65	9.85
Zambon et al.2000 (7)	1.28	0.61	2.68	7.99
Bosetti et al.2000 (14)	1.20	0.74	1.93	12.43
Lagergren et al.2000 (6)	0.46	0.17	1.20	5.57
Lee et al.2005 (15)	1.40	0.83	2.37	11.43
Freedman et al.2007 (45)	1.08	0.51	2.29	7.86
Hashibe et al.2007 (3)	0.32	0.09	1.16	3.58
Tanaka et al.2010 (11)	2.28	0.40	12.90	2.15
Szymanska et al.2011 (12)	0.42	0.18	0.98	6.68
Subtotal	0.96	0.73	1.25	
5-9 years				
Kabat et al.1993M (8)	0.40	0.20	0.80	11.58
Launoy et al.1997 (10)	0.69	0.33	1.45	10.06
Zambon et al.2000 (7)	0.69	0.36	1.31	13.21
Bosetti et al.2000 (14)	0.58	0.31	1.08	14.50
Lagergren et al.2000 (6)	0.43	0.17	1.09	6.53
Lee et al.2005 (15)	0.40	0.19	0.85	9.84
Freedman et al.2007 (45)	0.71	0.34	1.46	10.54
Hashibe et al.2007 (3)	0.89	0.40	1.97	8.81
Tanaka et al.2010 (11)	1.21	0.53	2.76	8.27
Szymanska et al.2011 (12)	0.32	0.13	0.80	6.65
Subtotal	0.59	0.47	0.75	
10-20 years				
Victora et al.1987 (40)	0.39	0.20	0.77	8.70
Kabat et al.1993M (8)	0.30	0.17	0.52	13.35
Castelletto et al.1994 (13)	0.50	0.20	1.22	5.02
Gammon et al.1997 (9)	0.45	0.23	0.88	9.24
Bosetti et al.2000 (14)	0.31	0.17	0.56	11.34
Lagergren et al.2000 (6)	0.29	0.13	0.63	6.72
De Stefani et al.2005 (5)	0.61	0.31	1.18	9.08
Hashibe et al.2007 (3)	0.30	0.13	0.71	5.50
Pandeya et al.2008 (2)	0.64	0.38	1.08	14.96
Steevens et al.2010 (1)	0.49	0.23	1.03	7.30
Szymanska et al.2011 (12)	0.45	0.23	0.89	8.80
Subtotal	0.42	0.34	0.51	
>20 years				
Victora et al.1987 (40)	0.48	0.25	0.91	9.23
Kabat et al.1993M (8)	0.20	0.12	0.35	10.21
Castelletto et al.1994 (13)	1.30	0.51	3.34	6.49
Gammon et al.1997 (9)	0.28	0.15	0.49	9.85
Bosetti et al.2000 (14)	0.31	0.20	0.49	11.32
Lagergren et al.2000 (6)	0.16	0.08	0.30	9.02
De Stefani et al.2005 (5)	0.70	0.36	1.33	9.16
Hashibe et al.2007 (3)	0.16	0.07	0.38	7.16
Pandeya et al.2008 (2)	0.40	0.26	0.60	11.68
Steevens et al.2010 (1)	0.56	0.25	1.24	7.71
Szymanska et al.2011 (12)	0.23	0.11	0.49	8.17
Subtotal	0.34	0.25	0.47	
Non-smokers				
Victora et al.1987 (40)	0.43	0.21	0.88	5.59
Kabat et al.1993M (8)	0.22	0.12	0.40	6.68
Kabat et al.1993F (8)	0.15	0.08	0.27	6.64
Castelletto et al.1994 (13)	0.40	0.21	0.75	6.32
Gammon et al.1997 (9)	0.20	0.11	0.36	6.61
Zambon et al.2000 (7)	0.17	0.10	0.28	7.30
Bosetti et al.2000 (14)	0.23	0.15	0.35	8.39
Lagergren et al.2000 (6)	0.10	0.06	0.19	6.39
De Stefani et al.2005 (5)	0.44	0.28	0.67	8.31
Freedman et al.2007 (45)	0.10	0.05	0.24	4.69
Hashibe et al.2007 (3)	0.13	0.07	0.25	6.22
Pandeya et al.2008 (2)	0.22	0.14	0.34	8.36
Steevens et al.2010 (1)	0.38	0.21	0.68	6.75
Tanaka et al.2010 (11)	0.26	0.13	0.53	5.68
Szymanska et al.2011 (12)	0.20	0.10	0.39	6.08
Subtotal	0.22	0.18	0.28	



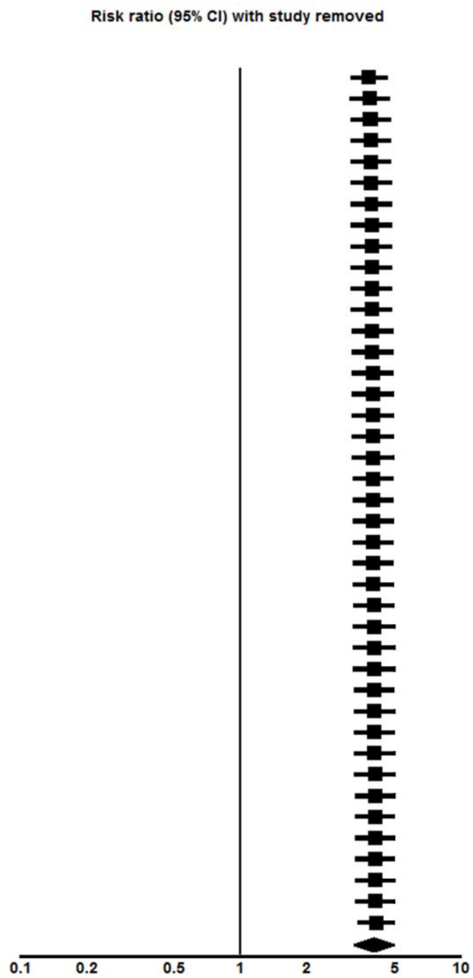
Supplementary Figure 2: Forest plot of risk ratio of esophageal squamous cell carcinoma among former smokers with current smokers as reference, stratified by smoking cessation years. The diamonds represent the effect sizes for the studies combined, the squares represent the effect sizes of individual studies and the weights given to the studies, and the error bars represent the corresponding 95% confidence intervals. CI=confidence interval.

Study name	Risk ratio	Lower limit	Upper limit
Venerito et al.2011 (16)	1.98	1.68	2.34
Wang et al.2013 (18)	1.99	1.68	2.36
Lee et al.2012 (36)	2.02	1.69	2.41
Tanaka et al.2010 (11)	2.02	1.69	2.41
Freedman et al.2007 (45)	2.02	1.69	2.42
Lee et al.2005 (15)	2.02	1.69	2.42
Bosetti et al.2000 (14)	2.03	1.69	2.43
Ishiguro et al.2009 (47)	2.03	1.69	2.43
Brown et al.1994 (17)	2.03	1.69	2.43
Wang et al.2007 (20)	2.03	1.70	2.43
Zambon et al.2000 (7)	2.03	1.69	2.44
Gammon et al.1997 (9)	2.03	1.70	2.44
Castelletto et al.1994 (13)	2.04	1.70	2.44
Bodelon et al.2011 (48)	2.04	1.70	2.44
Gledovic et al.2007 (31)	2.04	1.70	2.44
Lagergren et al.2000 (6)	2.04	1.70	2.45
Hashibe et al.2007 (3)	2.04	1.71	2.45
Wu et al.2006 (24)	2.05	1.71	2.45
Pandeya et al.2008 (2)	2.05	1.70	2.46
Kabat et al.1993F (8)	2.05	1.71	2.46
Chen et al.2011 (23)	2.05	1.71	2.46
Vaughan et al.1995 (27)	2.06	1.72	2.46
De Stefani et al.2005 (5)	2.06	1.71	2.47
Kollarova et al.2013 (34)	2.06	1.72	2.46
Lee et al.2009 (35)	2.06	1.72	2.47
Shivappa et al.2015 (21)	2.06	1.72	2.47
Szymanska et al.2011 (12)	2.06	1.72	2.47
Sewram et al.2003 (26)	2.07	1.72	2.48
De Stefani et al.1990 (25)	2.07	1.73	2.49
Steevens et al.2010 (1)	2.07	1.73	2.48
Victora et al.1987 (40)	2.08	1.73	2.48
Kabat et al.1993M (8)	2.08	1.74	2.49
Vioque et al.2008 (4)	2.08	1.74	2.49
Nasrollahzadeh et al.2008 (22)	2.08	1.74	2.49
Gao et al.2011 (29)	2.08	1.74	2.49
Mota et al.2013 (30)	2.08	1.74	2.49
Gallus et al.2001 (28)	2.09	1.75	2.50
Morita et al.2003 (32)	2.09	1.75	2.49
Zendehdel et al.2008 (46)	2.09	1.75	2.50
Lindblad et al.2005 (19)	2.11	1.77	2.51
Sharp et al.2001 (33)	2.14	1.81	2.53
Overall	2.05	1.72	2.45



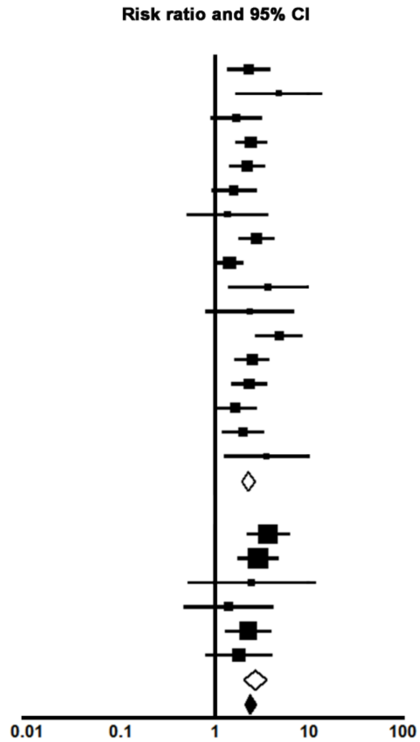
Supplementary Figure 3: Sensitivity analysis for risk ratio of esophageal squamous cell carcinoma in former smokers by one-study removed strategy. The diamonds represent the effect sizes for the studies combined, the squares represent the effect sizes of individual studies and the weights given to the studies, and the error bars represent the corresponding 95% confidence intervals. CI=confidence interval.

Study name	Risk ratio	Lower limit	Upper limit
Lee et al.2012 (36)	3.86	3.18	4.69
Venerito et al.2011 (16)	3.90	3.17	4.80
Brown et al.1994 (17)	3.92	3.18	4.82
Lagergren et al.2000 (6)	3.95	3.20	4.87
Bodelon et al.2011 (48)	3.95	3.20	4.87
Vaughan et al.1995 (27)	3.95	3.20	4.88
Freedman et al.2007 (45)	3.96	3.21	4.89
Zendehdel et al.2008 (46)	3.96	3.21	4.90
Kollarova et al.2013 (34)	3.97	3.21	4.90
Hashibe et al.2007 (3)	3.97	3.21	4.91
Bosetti et al.2000 (14)	3.97	3.21	4.92
Kabat et al.1993F (8)	3.98	3.22	4.92
Zambon et al.2000 (7)	3.99	3.22	4.94
Wu et al.2006 (24)	3.99	3.23	4.94
Gammon et al.1997 (9)	4.01	3.24	4.96
Szymanska et al.2011 (12)	4.01	3.24	4.97
Pandeya et al.2008 (2)	4.02	3.24	4.99
Kabat et al.1993M (8)	4.02	3.25	4.98
Lee et al.2005 (15)	4.03	3.25	5.00
Lee et al.2009 (35)	4.03	3.25	4.99
Mota et al.2013 (30)	4.04	3.26	5.00
Victora et al.1987 (40)	4.04	3.26	5.00
Tanaka et al.2010 (11)	4.04	3.26	5.00
Ishiguro et al.2009 (47)	4.04	3.26	5.01
Gallus et al.2001 (28)	4.05	3.26	5.02
Wang et al.2013 (18)	4.06	3.24	5.09
Gledovic et al.2007 (31)	4.06	3.28	5.04
Castelletto et al.1994 (13)	4.06	3.28	5.03
Sewram et al.2003 (26)	4.07	3.28	5.06
Steevens et al.2010 (1)	4.08	3.29	5.05
Vioque et al.2008 (4)	4.08	3.30	5.04
De Stefani et al.1990 (25)	4.09	3.30	5.07
De Stefani et al.2005 (5)	4.10	3.31	5.07
Morita et al.2003 (32)	4.11	3.32	5.08
Wang et al.2007 (20)	4.12	3.34	5.09
Chen et al.2011 (23)	4.12	3.34	5.09
Nasrollahzadeh et al.2008 (22)	4.13	3.34	5.10
Lindblad et al.2005 (19)	4.13	3.35	5.10
Shivappa et al.2015 (21)	4.13	3.35	5.10
Sharp et al.2001 (33)	4.13	3.35	5.10
Gao et al.2011 (29)	4.17	3.41	5.09
Overall	4.03	3.27	4.97



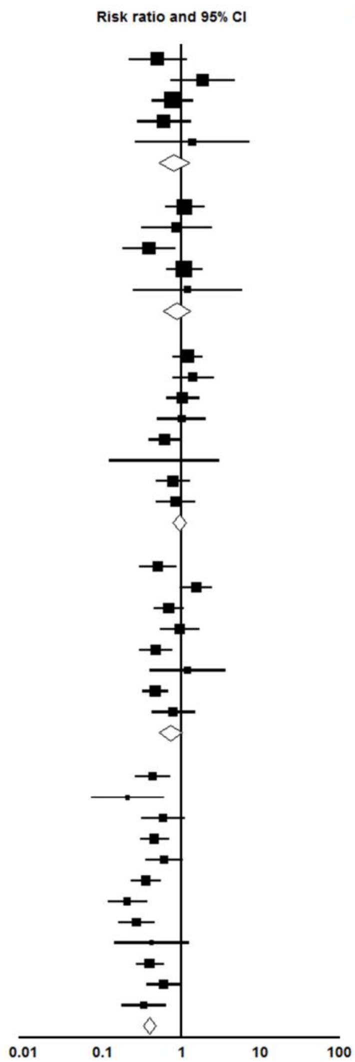
Supplementary Figure 4: Sensitivity analysis for risk ratio of esophageal squamous cell carcinoma in current smokers by one-study removed strategy. The diamonds represent the effect sizes for the studies combined, the squares represent the effect sizes of individual studies and the weights given to the studies, and the error bars represent the corresponding 95% confidence intervals. CI=confidence interval.

Study	Risk ratio	Lower limit	Upper limit	Relative weight
Case-control				
Kabat et al.1993M (8)	2.30	1.38	3.84	6.55
Kabat et al.1993F (8)	4.80	1.67	13.77	2.09
Brown et al.1994 (38)	1.70	0.90	3.21	4.85
Vaughan et al.1995 (27)	2.43	1.66	3.57	9.20
Gammon et al.1997 (9)	2.20	1.43	3.38	8.16
Lagergren et al.2000 (6)	1.60	0.92	2.77	5.96
Cheng et al.2000 (41)	1.37	0.51	3.69	2.33
Wu et al.2001 (37)	2.80	1.81	4.33	8.01
Lindblad et al.2005 (19)	1.45	1.06	1.99	11.09
De Jonge et al.2006 (44)	3.70	1.39	9.84	2.39
Hashibe et al.2007 (3)	2.38	0.80	7.06	1.98
Anderson et al.2007 (39)	4.84	2.72	8.61	5.57
Pandeya et al.2008 (2)	2.51	1.65	3.81	8.42
Bradbury et al.2009 (43)	2.35	1.52	3.62	8.09
Steevens et al.2010 (1)	1.67	1.01	2.77	6.68
Xu et al.2013 (42)	2.01	1.19	3.37	6.45
Kollarova et al.2013 (34)	3.53	1.26	9.88	2.18
Subtotal	2.24	1.91	2.64	
Cohort				
Freedman et al.2007 (45)	3.70	2.20	6.22	26.65
Zendehdel et al.2008 (46)	2.90	1.78	4.74	29.93
Bodelon et al.2011 (48)	2.49	0.52	11.95	2.93
Sikkema et al.2011 (51)	1.40	0.47	4.15	6.09
Coleman et al.2012 (52)	2.29	1.32	3.99	23.42
Yates et al.2014 (50)	1.82	0.81	4.09	10.98
Subtotal	2.65	2.03	3.46	
Overall	2.34	2.04	2.69	

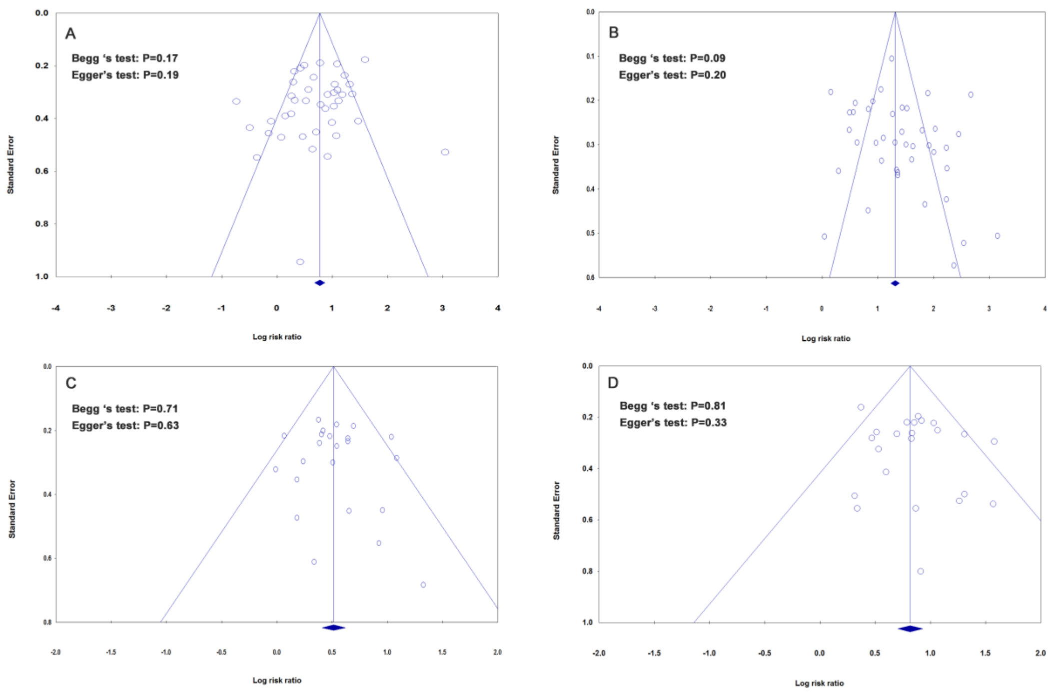


Supplementary Figure 5: Forest plot of risk ratio of esophageal adenocarcinoma among current smokers with non-smokers as reference, stratified by study design. The diamonds represent the effect sizes for the studies combined, the squares represent the effect sizes of individual studies and the weights given to the studies, and the error bars represent the corresponding 95% confidence intervals. CI=confidence interval.

Smoking cessation	Risk ratio	Lower limit	Upper limit	Relative weight
<5 years				
Kabat et al.1993M (8)	0.50	0.21	1.17	20.42
Lagergren et al.2000 (6)	1.87	0.73	4.82	17.39
Wu et al.2001 (37)	0.77	0.42	1.41	32.91
Freedman et al.2007 (45)	0.60	0.27	1.32	22.79
Hashibe et al.2007 (3)	1.38	0.26	7.31	6.49
Subtotal	0.81	0.52	1.26	
5-9 years				
Kabat et al.1993M (8)	1.10	0.62	1.96	29.37
Lagergren et al.2000 (6)	0.86	0.31	2.43	12.69
Wu et al.2001 (37)	0.39	0.18	0.85	19.95
Freedman et al.2007 (45)	1.09	0.64	1.86	32.05
Hashibe et al.2007 (3)	1.19	0.24	5.86	5.95
Subtotal	0.87	0.58	1.30	
10-20 years				
Kabat et al.1993M (8)	1.20	0.78	1.85	21.09
Brown et al.1994 (38)	1.41	0.77	2.58	10.81
Gammon et al.1997 (9)	1.04	0.64	1.71	16.03
Lagergren et al.2000 (6)	1.01	0.50	2.07	7.72
Wu et al.2001 (37)	0.62	0.38	1.03	15.75
Hashibe et al.2007 (3)	0.60	0.12	3.01	1.51
Pandeya et al.2008 (2)	0.79	0.48	1.31	15.43
Steevens et al.2010 (1)	0.84	0.47	1.51	11.65
Subtotal	0.95	0.78	1.15	
>20 years				
Kabat et al.1993M (8)	0.50	0.29	0.87	12.76
Brown et al.1994 (38)	1.55	0.97	2.48	14.07
Gammon et al.1997 (9)	0.69	0.44	1.09	14.39
Lagergren et al.2000 (6)	0.95	0.53	1.71	12.18
Wu et al.2001 (37)	0.47	0.29	0.78	13.59
Hashibe et al.2007 (3)	1.19	0.39	3.62	6.13
Pandeya et al.2008 (2)	0.46	0.31	0.68	15.53
Steevens et al.2010 (1)	0.79	0.42	1.49	11.36
Subtotal	0.72	0.52	1.01	
Non-smokers				
Kabat et al.1993M (8)	0.43	0.26	0.72	9.45
Kabat et al.1993F (8)	0.21	0.07	0.60	2.97
Brown et al.1994 (38)	0.59	0.31	1.11	6.96
Gammon et al.1997 (9)	0.45	0.30	0.70	11.84
Lagergren et al.2000 (6)	0.60	0.35	1.03	8.80
Wu et al.2001 (37)	0.36	0.23	0.55	11.63
Anderson et al.2007 (39)	0.21	0.12	0.37	8.02
Freedman et al.2007 (45)	0.27	0.16	0.45	9.21
Hashibe et al.2007 (3)	0.42	0.14	1.25	2.80
Pandeya et al.2008 (2)	0.40	0.26	0.60	12.24
Steevens et al.2010 (1)	0.59	0.36	0.99	9.60
Ramus et al.2012 (49)	0.33	0.17	0.65	6.46
Subtotal	0.40	0.33	0.48	



Supplementary Figure 6: Forest plot of risk ratio of esophageal adenocarcinoma among former smokers with current smokers as reference, stratified by smoking cessation years. The diamonds represent the effect sizes for the studies combined, the squares represent the effect sizes of individual studies and the weights given to the studies, and the error bars represent the corresponding 95% confidence intervals. CI=confidence interval.



Supplementary Figure 7: Funnel plots and Begg's and Egger's tests detecting publication bias. A) Risk of esophageal squamous cell carcinoma in former smokers; **B**) Risk of esophageal squamous cell carcinoma in current smokers. **C**) Risk of esophageal adenocarcinoma in former smokers. **D**) Risk of esophageal adenocarcinoma in current smokers. All P values are from two-sided tests.

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Table 1 Tobacco smoking status and risk of esophageal squamous cell carcinoma, using non-smokers as the reference.

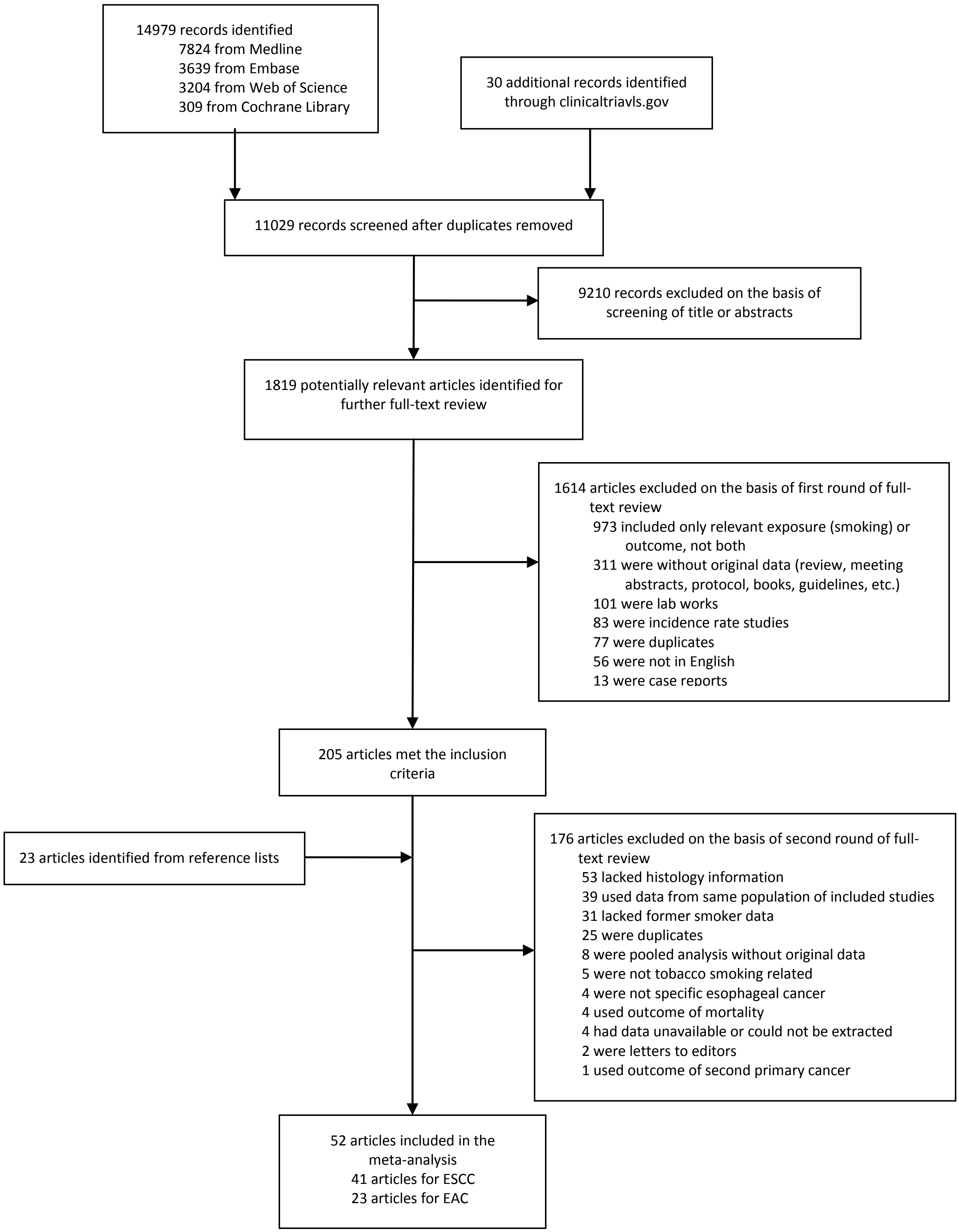
Study characteristics	Former smokers				Current smokers			
	Risk Ratio (95% CI)	Studies (n)	$P_{heterogeneity}$*	I^2(%)†	Risk Ratio (95% CI)	Studies (n)	$P_{heterogeneity}$*	I^2(%)†
Overall	2.05 (1.71-2.45)	41	<.001	69.6	4.18 (3.42-5.12)	41	<.001	85.0
Study design								
Case-control	2.01 (1.67-2.43)	37	<.001	70.4	3.81 (3.06-4.74)	37	<.001	85.6
Cohort	2.50 (1.29-4.85)	4	.03	66.2	6.95 (4.17-11.57)	4	.10	52.9
Publication year								
≤1999	1.98 (1.54-2.54)	8	.26	21.7	5.07 (3.35-7.68)	8	<.001	75.3
2000-2009	1.85 (1.47-2.34)	21	<.001	67.8	3.62 (2.83-4.64)	21	<.001	79.5
≥2010	2.57 (1.69-3.91)	12	<.001	78.7	4.29 (2.54-7.24)	12	<.001	91.8
Geographic origin								
North America	2.45 (1.83-3.27)	7	.31	16.3	5.75 (3.56-9.26)	7	.002	70.7
Europe	1.75 (1.15-2.65)	14	<.001	79.3	4.57 (3.19-6.54)	14	<.001	81.5
Oceania	2.18 (1.51-3.17)	1	1.00	0.0	4.58 (2.99-7.02)	1	1.00	0.0
Asia	2.47 (1.78-3.44)	12	<.001	72.6	2.82 (1.81-4.39)	12	<.001	91.5
South America	1.67 (1.37-2.04)	7	.67	0.0	2.91 (2.41-3.50)	7	.47	0.0
Sex‡								
Men	2.00 (1.43-2.80)	10	.01	57.2	3.77 (2.29-6.20)	10	<.001	85.7
Women	1.34 (0.71-2.53)	6	.006	69.1	3.85 (2.20-6.74)	6	.003	72.2
Unspecified	2.26 (1.86-2.76)	29	<.001	66.9	3.94 (3.12-4.99)	29	<.001	84.0
Response rate								
≥80%	1.92 (1.56-2.36)	15	.05	40.6	4.21 (2.74-6.47)	15	<.001	90.4
<80%	2.42 (1.70-3.45)	10	<.001	70.1	4.80 (3.09-7.43)	10	<.001	83.2
Unknown	1.95 (1.36-2.78)	16	<.001	79.3	3.51 (2.69-4.60)	16	<.001	76.9
Smoking exposure								
Main exposure	1.88 (1.57-2.24)	33	<.001	60.6	3.97 (3.17-4.96)	33	<.001	81.3
Confounder	3.08 (1.90-4.98)	8	<.001	81.2	4.35 (2.44-7.76)	8	<.001	92.7
Tobacco types								
Cigarettes	2.38 (1.58-3.60)	15	<.001	82.8	4.02 (3.07-5.28)	15	<.001	72.7
Unspecified	1.94 (1.66-2.26)	26	.01	41.9	3.96 (2.94-5.33)	26	<.001	88.4
Study quality								
Low (score<7)	2.16 (1.63-2.86)	19	<.001	74.8	3.60 (2.65-4.90)	19	<.001	87.0
High (score≥7)	1.97 (1.57-2.48)	22	<.001	64.7	4.45 (3.31-5.99)	22	<.001	83.5
Adjusted variables								

Alcohol use								
Yes	2.09 (1.72-2.54)	22	.02	42.3	4.59 (3.67-5.74)	19	<.001	60.1
No	2.05 (1.52-2.76)	19	<.001	81.1	3.54 (2.56-4.88)	21	<.001	90.6
Dietary factors								
Yes	1.76 (1.20-2.58)	12	<.001	71.0	4.42 (3.11-6.28)	11	.001	67.6
No	2.17 (1.78-2.66)	29	<.001	69.4	3.91 (3.04-5.03)	30	<.001	87.6
Socio-economy								
Yes	2.07 (1.73-2.49)	18	.11	30.0	4.19 (3.20-5.48)	16	<.001	70.9
No	2.04 (1.54-2.70)	23	<.001	79.4	3.93 (2.93-5.27)	25	<.001	88.8
Place of residence								
Yes	2.02 (1.67-2.45)	20	.01	46.5	3.78 (2.85-5.01)	19	<.001	79.3
No	2.09 (1.55-2.82)	21	<.001	78.9	4.26 (3.14-5.79)	22	<.001	88.1
Case-control study								
Study design								
Population-based	1.66 (1.19-2.30)	11	<.001	71.3	3.23 (1.98-5.29)	11	<.001	90.4
Hospital-based	2.21 (1.77-2.75)	26	<.001	68.0	4.10 (3.26-5.15)	26	<.001	80.6
Cases recruitment								
Incident	2.20 (1.78-2.73)	28	<.001	73.4	4.21 (3.28-5.40)	28	<.001	86.1
Prevalent	1.49 (1.01-2.19)	7	.08	47.3	2.90 (1.77-4.75)	7	<.001	83.1
Unknown	1.32 (0.73-2.38)	2	.60	0.0	2.11 (0.58-7.61)	2	.04	77.4
Source of controls								
Unrelated	2.07 (1.71-2.51)	35	<.001	70.1	4.05 (3.28-5.01)	35	<.001	82.9
Neighborhood	1.36 (0.98-1.89)	2	.95	0.0	1.30 (0.96-1.77)	2	.30	5.3
Cohort study								
Study design								
Population-based	3.46 (2.26-5.31)	3	.79	0.0	6.98 (3.19-15.28)	3	.06	65.6
Occupation-based	0.90 (0.40-2.00)	1	1.00	0.0	7.60 (4.50-12.70)	1	1.00	0.0
Follow-up time								
<10 years	4.35 (1.95-9.72)	1	1.00	0.0	9.27 (4.04-21.29)	1	1.00	0.0
≥10 years	2.08 (0.92-4.70)	3	.03	70.4	6.51 (3.42-12.42)	3	.06	64.0
Outcome assessment								
Record linkage	2.37 (0.98-5.77)	3	.01	77.2	6.16 (3.56-10.66)	3	.10	56.2
Self-reported	2.93 (1.18-7.32)	1	1.00	0.0	12.67 (4.55-35.28)	1	1.00	0.0

* P-values from two-sided Cochran's Q test. Abbreviation: CI: confidence intervals.

† I^2 statistics indicating the percentage of variation across studies that is due to heterogeneity.

‡Two studies (Stefani et al.1990 and Victora et al.2007) reported risk ratio for men and women separately and combined; one study (Kabat et al.1993) reported risk ratio for men and women separately.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7824 from Medline
3639 from Embase
3204 from Web of Science
309 from Cochrane Library
30 additional records identified through clinicaltriavls.gov
11029 records screened after duplicates removed
9210 records excluded on the basis of screening of title or abstracts
1819 potentially relevant articles identified for further full-text review
1614 articles excluded on the basis of first round of full-text review
973 included only relevant exposure (smoking) or outcome, not both
311 were without original data (review, meeting abstracts, protocol, books, guidelines, etc.)
101 were lab works
83 were incidence rate studies
77 were duplicates
56 were not in English
13 were case reports
205 articles met the inclusion criteria
23 articles identified from reference lists
176 articles excluded on the basis of second round of full-text review
53 lacked histology information
39 used data from same population of included studies
31 lacked former smoker data
25 were duplicates
8 were pooled analysis without original data
5 were not tobacco smoking related
4 were not specific esophageal cancer
4 used outcome of mortality
4 had data unavailable or could not be extracted
2 were letters to editors
1 used outcome of second primary cancer
52 articles included in the meta-analysis
41 articles for ESCC
23 articles for EAC

Figure 2

Study	Risk ratio	Lower limit	Upper limit	Relative weight
Case-control				
Victora et al.1987 (37)	1.29	0.61	2.73	2.50
De Stefani et al.1990 (38)	1.53	1.01	2.30	3.49
Kabat et al.1993M (39)	1.30	0.70	2.41	2.87
Kabat et al.1993F (39)	2.20	1.11	4.35	2.68
Castelletto et al.1994 (41)	2.80	1.40	5.60	2.65
Brown et al.1994 (40)	2.99	1.69	5.29	3.01
Vaughan et al.1995 (42)	1.90	0.69	5.23	1.87
Gammon et al.1997 (26)	2.80	1.55	5.06	2.95
Lagergren et al.2000 (46)	2.50	1.36	4.58	2.91
Zambon et al.2000 (47)	2.85	1.68	4.83	3.13
Bosetti et al.2000 (44)	2.97	2.03	4.33	3.58
Gallus et al.2001 (48)	0.86	0.35	2.10	2.13
Sharp et al.2001 (49)	0.48	0.25	0.93	2.76
Sewram et al.2003 (52)	1.63	1.11	2.41	3.55
Morita et al.2003 (51)	0.69	0.24	2.03	1.75
De Stefani et al.2005 (53)	1.94	1.20	3.12	3.29
Lee et al.2005 (54)	3.40	2.14	5.40	3.33
Lindblad et al.2005 (55)	0.61	0.26	1.43	2.23
Wu et al.2006 (57)	2.50	0.86	7.26	1.76
Hashibe et al.2007 (59)	2.40	1.18	4.89	2.60
Wang et al.2007 (60)	3.05	1.59	5.85	2.77
Gledovic et al.2007 (58)	2.70	1.20	6.09	2.33
Pandeya et al.2008 (28)	2.18	1.50	3.16	3.60
Vioque et al.2008 (62)	1.08	0.43	2.72	2.06
Nasrollahzadeh et al.2008 (61)	1.34	0.80	2.24	3.18
Lee et al.2009 (66)	1.77	1.00	3.13	3.01
Steevens et al.2010 (67)	1.38	0.72	2.64	2.78
Tanaka et al.2010 (27)	3.90	2.14	7.12	2.92
Szymanska et al.2011 (72)	1.69	0.88	3.24	2.77
Venerito et al.2011 (73)	21.03	7.48	59.16	1.83
Chen et al.2011 (69)	2.03	0.84	4.92	2.15
Gao et al.2011 (70)	1.37	0.89	2.11	3.42
Lee et al.2012 (75)	3.73	2.19	6.33	3.13
Wang et al.2013 (78)	4.92	3.48	6.96	3.66
Mota et al.2013 (77)	1.16	0.54	2.49	2.46
Kollarova et al.2013 (24)	1.52	0.24	9.67	0.81
Shivappa et al.2015 (81)	1.60	0.64	4.00	2.07
Subtotal	2.01	1.67	2.43	
Cohort				
Freedman et al.2007 (9)	4.35	1.95	9.71	24.47
Zendehdel et al.2008 (63)	0.90	0.40	2.01	24.44
Ishiguro et al.2009 (65)	3.27	1.78	6.00	28.92
Bodelon et al.2011 (68)	2.93	1.18	7.30	22.17
Subtotal	2.50	1.29	4.85	
Overall	2.05	1.71	2.45	

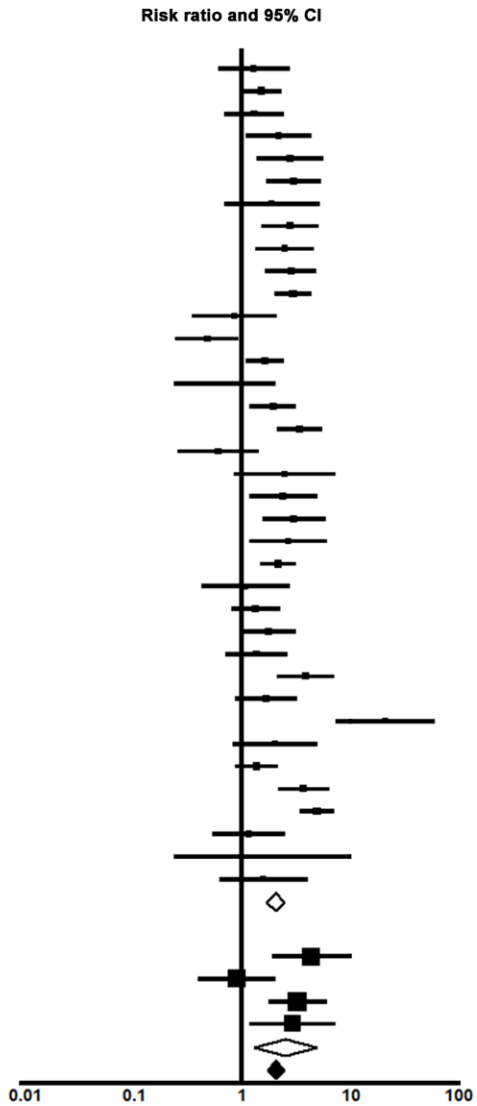
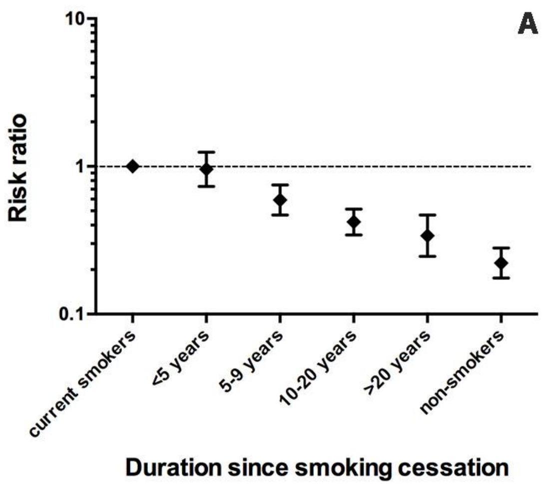
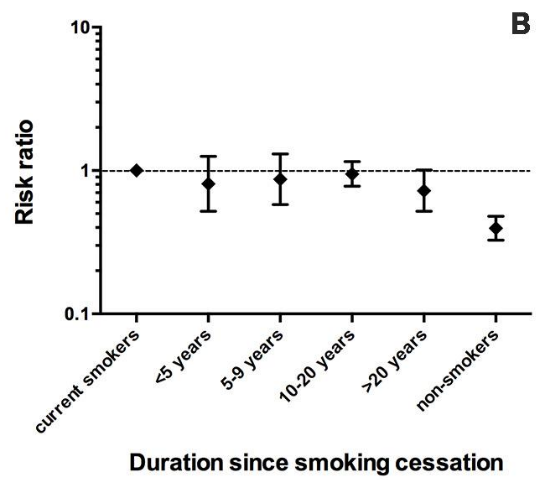


Figure 3



A
10
1
0.1
Risk ratio
current smokers
<5 years
5-9 years
10-20 years
>20 years
non-smokers
Duration since smoking cessation



B
10
1
0.1
Risk ratio
current smokers
<5 years
5-9 years
10-20 years
>20 years
non-smokers
Duration since smoking cessation

Figure 4

Study	Risk ratio	Lower limit	Upper limit	Relative weight
Case-control				
Kabat et al.1993M (39)	1.90	1.20	3.00	6.37
Kabat et al.1993F (39)	1.40	0.42	4.64	0.98
Brown et al.1994 (29)	2.96	1.69	5.19	4.33
Vaughan et al.1995 (42)	1.50	0.99	2.27	7.62
Gammon et al.1997 (26)	2.00	1.39	2.88	9.77
Lagergren et al.2000 (46)	1.90	1.22	2.95	6.84
Cheng et al.2000 (45)	0.99	0.53	1.86	3.46
Wu et al.2001 (50)	1.52	1.02	2.25	8.44
Lindblad et al.2005 (55)	1.07	0.70	1.64	7.31
De Jonge et al.2006 (56)	2.60	1.08	6.27	1.80
Hashibe et al.2007 (59)	2.52	0.85	7.45	1.19
Anderson et al.2007 (23)	1.72	1.06	2.80	5.66
Pandeya et al.2008 (28)	1.46	1.05	2.03	11.86
Bradbury et al.2009 (64)	1.72	1.20	2.45	10.22
Steevens et al.2010 (67)	1.47	0.92	2.35	6.10
Xu et al.2013 (79)	1.61	1.05	2.47	7.28
Kollarova et al.2013 (24)	3.77	0.99	14.40	0.78
Subtotal	1.65	1.47	1.86	
Cohort				
Freedman et al.2007 (9)	2.82	1.83	4.34	26.34
Zendehdel et al.2008 (63)	1.20	0.60	2.40	15.23
Bodelon et al.2011 (68)	1.92	0.79	4.66	10.60
Sikkema et al.2011 (71)	1.20	0.47	3.04	9.85
Coleman et al.2012 (74)	1.66	0.92	2.99	18.83
Yates et al.2014 (80)	1.27	0.71	2.27	19.15
Subtotal	1.70	1.23	2.35	
Overall	1.66	1.48	1.85